UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: February 7, 2002

SUBJECT: **Imazalil**: HED Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Chemical No. 111901. Reregistration Case No. 2325, Barcode D280708

FROM: Abdallah Khasawinah, Risk Assessor
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THROUGH: Susan Hummel, Branch Senior Scientist
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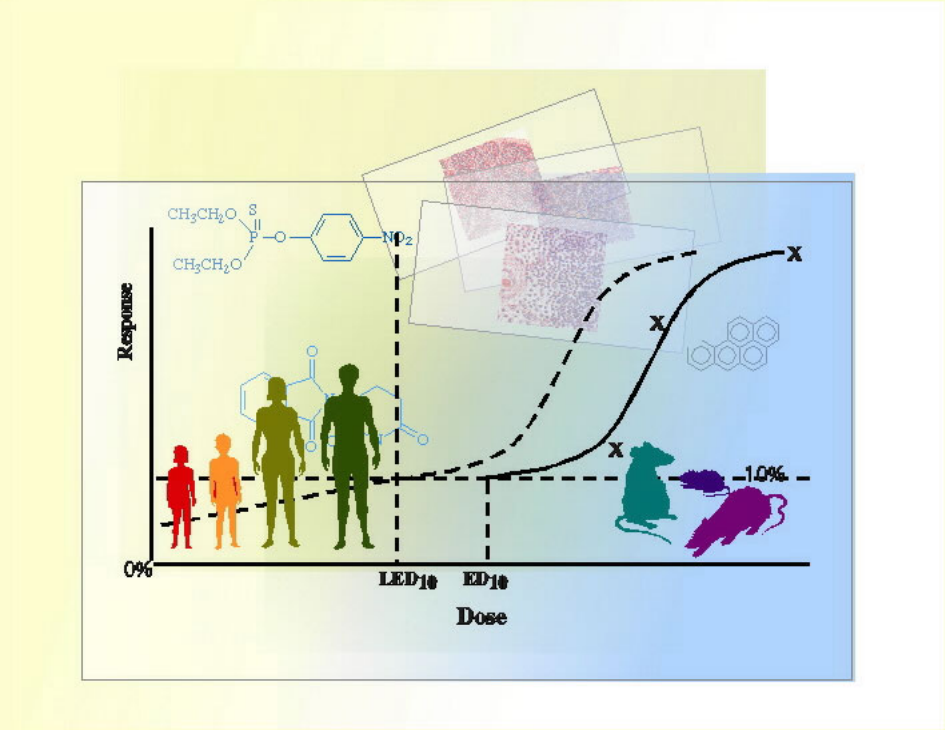
TO: Dayton Eckerson/Dan Helfgott
Special Review Branch
Special Review and Reregistration Division (7508W)

Attached is HED's risk assessment of the fungicide, imazalil for the purposes of issuing a Reregistration Eligibility Decision (RED) Document for the active ingredient. Cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity is not addressed in this document. The disciplinary science chapters and other supporting documents for the imazalil RD are also included as attachments as follows:

Report of the Hazard Identification Assessment Review Committee. Abdallah Khasawinah (6/29/1999, HED DOC #013539)
Report of the FQPA Safety Factor Committee. Brenda Tarplee (9/28/1999, HED DOC #013762)
Report of the Cancer Assessment Review Committee- Imazalil. SanJivani Diwan (12/7/99, HED DOC #013885)
Product and Residue Chemistry Chapter. Thurston Morton, David E. Hrdy (1/31/2002, D272790)
Toxicology Chapter. Abdallah Khasawinah (1/31/2002, HED DOC# 0050434)
Occupational and Residential Exposure Assessment. Seyed Tadayan 124/25/2000, D270918)
Dietary Exposure and Risk Estimates for Reregistraiton. Thurston Morton, David E. Hrdy (1/24/2002, D280449)
Environmental Fate and Effects Chapter. Larry Liu and Richard Lee (2000, D250028)

HUMAN HEALTH RISK ASSESSMENT

Imazalil



U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)
Abdallah Khasawinah, Risk Assessor
Date: January 16, 2002

HUMAN HEALTH RISK ASSESSMENT

Imazalil

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I. EXECUTIVE SUMMARY

A. Use and Major Formulations

Imazalil [1-(2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl)-1*H*-imidazole] is a systemic fungicide registered for post-harvest treatment of citrus fruits and bananas (import tolearance only) and for seed treatment of barley and wheat prior to planting. Imazalil is also used in egg handling facilities. The reregistration of imazalil is being supported by Janssen Pharmaceutica and Makhteshim-Agan of North America Inc. (MANA).

Imazalil is used to prevent, treat and control diseases caused by a variety of pathogenic organisms (fungi), which include (but are not limited to) *Aspergillus* in egg handling facilities and equipment, blue mold in citrus fruits and *Fusarium* in wheat and barley seeds. **There are no current registered uses for recreational, residential or other public (non-commercial) settings.** Use sites include terrestrial food and feed crop (barley, wheat), terrestrial feed crop (sudan grass), indoor food (post-harvest treatment of citrus fruits), and indoor non-food (egg hatching equipment, egg hatching rooms and air ducts). A wide variety of application techniques have been identified that could potentially be used for imazalil such as seed treatment, drenches, smoke generators, fruit waxing equipment and hand held equipment.

B. Regulatory History

Imazalil is a List B reregistration pesticide. Imazalil was first registered by Janssen Pharmaceutica (FIFRA Section 3) as technical manufacturing use product (Fungaflor technical) on July 13, 1983 and as an end use product (Fungaflor) on July 18, 1983. Since then, imazalil has continuously had one or more FIFRA Section 3 for postharvest use on citrus fruits against various fungi. According to the EPA OPP REFS label tracking system, there are 15 active labels including two technical grade (Magnate technical 98.50-98.94% active ingredient), one impregnated material (14.9% a.i.), 4 liquids (up to 31% a.i.), seven emulsifiable concentrates (up to 68.25% a.i.), and a flowable concentrate (10 % a.i.). Currently water soluble packets are not marketed. Impregnated material is used in smoke generators.

Several Experimental Use Permits (EUPs) have been issued for imazalil products. On January 29, 1985 an EUP was issued to Elf Atochem N.A., Inc. for research on the use of Imazalil on Melons. On January 29, 1985 two EUPs were issued to Janssen Pharmaceutica for research on the use of Imazalil on Cucurbits, Tomatoes, and Peppers. On January 3, 1986 two EUPs were issued to Schering-Plough Animal Health to research the use of Imazalil in controlling fungi in poultry hatcheries.

Imazalil has not been subjected to a registration standard (because it is on List B) or any regulatory special review.

C. Hazard Identification and Dose Reponse Assessment

The toxicological data base for Imazalil is partly adequate for hazard characterization. Data gaps exist for an acute, subchronic and developmental neurotoxicity studies in rats. In acute toxicity studies imazalil, is moderately toxic by the oral route (Category II), and is of low toxicity by the dermal (Category III) and inhalation routes (Category IV). It is a severe eye irritant (Category I) but not a dermal irritant (Category IV) or a skin sensitizer. Acute toxic effects are lethargy, ptosis (drooping of the upper eyelids), decreased respiratory rate and gasping respiration, and ataxia.

The toxicity endpoints used in this document to assess hazards include acute dietary and chronic dietary reference doses (RfDs), and short-, intermediate- and long-term dermal and inhalation no observable adverse affect levels (NOAELs)

The thyroid and the liver are primary target organs of imazalil toxicity. Enlarged livers were seen in rabbits after 6 days of dermal application at 250 mg/kg/day, increased liver weights and liver to body weight ratios, increased centrilobular swollen hepatocytes and increased vacuolization in hepatocytes after one month of dietary treatment at 32 mg/kg/day in rats and similar histopathologic effects in mice at 39 mg/kg/day in the diet. In chronic dietary exposure of rats, there was an increased incidence of intra cytoplasmic inclusion bodies of hepatocytes, increased severity of hepatocyte vacuolization as well as bile duct proliferation at 16 mg/kg/day. Liver histopathologic lesions were also seen in a 23-month study in mice at 28 mg/kg/day. Increased liver vacuolization was also seen in male rats in a 2-generation reproduction study at 80 mg/kg/day. Increased liver weights were seen in dogs treated for one year at 20 mg/kg/day. The absolute and relative weight of thyroid glands was increased in male rats fed imazalil for two years at $\geq$66 mg/kg/day. Microscopic changes were also seen in the affected thyroids.

The data submitted to the Agency as well as those from the published literature do not demonstrate increased sensitivity of rats, mice, or rabbits from *in utero* exposure to imazalil. Developmental effects in fetuses occurred at or above doses that caused maternal toxicity. In a 2-generation reproduction study in rats, an increased susceptibility of the pups to imazalil was reported. The pup survival rate was adversely affected by imazalil treatment from birth to post natal day 4 in the F2 generation at the highest tested dose of 80 mg/kg/day. The Hazard Identification Assessment Review Committee (HIARC) determined that pup deaths resulted from an increased susceptibility to imazalil from the milk intake during lactation.

Carcinogenicity studies in rodents indicate that imazalil is carcinogenic to male Swiss albino mice and male Wistar rats, based on a significant increase in liver adenomas and combined adenomas/carcinomas. In rats there was also an increased incidence of combined thyroid follicular cell adenomas/carcinomas. Imazalil is classified by the CARC in the category "Likely to be carcinogenic in humans" according to the July 1999 Draft Guidelines for Carcinogenic Assessment. The Committee reaffirmed its earlier decision by recommending a linear low-dose (Q_1^*) extrapolation for quantification of human cancer risk. This extrapolation is supported by the lack of confirmation of the mode of action. The most potent unit risk, $Q_1^*(mg/kg/day)^{-1}$ for imazalil based on male mouse liver adenoma and/or carcinoma combined tumor rates is 6.1 x 10^{-2} $(mg/kg/day)^{-1}$ in human equivalents (HED Doc 013842).

Imazalil was non mutagenic both *in vivo* and *in vitro* mutagenicity assays.

The Food Quality Protection Act (FQPA) Safety Factor Committee (SFC) evaluated imazalil toxicity and exposure databases and retained a 10x FQPA Safety Factor for assessing chronic dietary exposure and reduced it to 3x for acute scenarios. The FQPA SFC concluded that the full safety factor of 10 should be retained for chronic exposure scenarios because of qualitative evidence of increased susceptibility following pre-/postnatal exposure to imazalil in the 2-generation reproduction study in rats and because of a data gap for a developmental neurotoxicity study. Although there was a lack of evidence of susceptibility in the rat/rabbit developmental studies, the data gap for a developmental neurotoxicity study was also considered to apply for acute scenarios, and accordingly the SFC did not completely remove the FQPA factor but reduced it to 3x for acute scenarios.

D. Exposure Assessment

The qualitative nature of the residue of imazalil in plants and animals is adequately understood. The residue of concern in plants is imazalil with minor amounts of metabolites containing the 2,4-dichlorophenyl group; the established tolerance expression for residues of imazalil in/on plant commodities is appropriate. The imazalil residues of concern in livestock include imazalil and any imazalil metabolite containing the 2,4-dichlorophenyl moiety.

The established tolerances for residues of imazalil in/on plant commodities [40 CFR §180.413(a)] are expressed in terms of the combined residues of imazalil and its metabolite R014821 [1-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-yl)-1-ethanol]. Plant commodity tolerances range from 0.05 ppm (barley grain, cottonseed, and wheat grain) to 10 ppm (citrus fruits). Tolerances are also established for the combined residues of imazalil and R014821 in citrus oil and citrus dried pulp, each at 25 ppm. The established tolerances for residues of imazalil in livestock commodities [40 CFR §180.413(b)] are expressed in terms of the combined residues of imazalil and its metabolites R014821 and R042243 [3-[1-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-yl)ethoxyl]-1,2-propanediol]. Livestock commodity tolerances range from 0.01 ppm (milk and fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep) to 0.50 ppm (liver of cattle, goats, hogs, horses, and sheep). No tolerances are established for residues in eggs or poultry tissues. Residues of concern in plants include imazalil and its metabolite R014821. The HED Metabolism Committee (L. Cheng, 8/30/94) concluded that imazalil residues to be regulated in livestock commodities will include imazalil and any metabolite containing the 2,4-dichlorophenyl moiety.

The Biological and Economic Analysis Division (OPP/BEAD) has provided usage information for imazalil (J. Alsadek, 11/5/01). USDA Pesticide Data Program (PDP) data (1994-1999) reflected analysis for imazalil only (i.e. metabolite residues were not quantified). HED used the PDP data which analyzed for imazalil only and adjusted the residues to account for the additional residues of concern. An adjustment factor was derived from nature of the residue studies in plants submitted by the registrant. Total radioactive residues were less than 0.004 ppm in the wheat metabolism study (L. Cheng, D187506, 1/5/94); therefore, wheat PDP data for

parent were used without adjusting for metabolites. Total radioactive residues were less than 0.003 ppm in banana pulp from the banana metabolism study (L. Cheng, D224876, 6/11/96); therefore, banana PDP data for parent were used without adjusting for metabolites. A factor of 1.4 to convert the orange PDP data to account for metabolite R014821 residues in orange pulp was calculated from the nature of the residue study in oranges (L. Cheng, D198235, 4/28/94). The orange pulp TRR data were used since PDP peels the orange samples before analysis. PDP samples of milk were analyzed for imazalil only and showed no detectable residues of parent in 692 samples. Imazalil and residues of the marker metabolites were all <0.06 ppm the limit of quantitation (LOQ) in milk in the metabolism study (F. Suhre, D182706, 2/16/93). Total imazalil residues after adjusting for marker metabolite concentrations were less than the reported LOQ of 0.06 ppm (0.02 ppm for each compound) in the 5x feeding level of the ruminant feeding study (S. Piper, D245510, 1/22/99) when normalized to the 1x feeding level. Therefore, milk food forms were considered to be negligible or zero, and were excluded from the dietary exposure analysis. For anticipated residues using PDP data, half the Limit of Detection (LOD) value was a weighted average of all laboratory LODs. Bananas had PDP monitoring data which contained over-tolerance residues. These values were removed in the undecomposited residue distribution file (per HED Dietary Exposure Science Advisory Council policy) since no clear pattern of over-tolerance residues was occurring. In addition, when decompositing the PDP data for bananas, over-tolerance values resulted. In accordance with HED policy, these over-tolerance values were "set back" to the tolerance of 0.2 ppm.

For non-blended food forms (NB), single unit residue values were included in the residue distribution file (RDF) for the acute analysis; these single unit residues were statistically generated by way of decomposition of composite PDP residue values using the method described in the H. Allender paper (5/26/99) titled "Statistical Methods for Use of Composite Data in Acute Dietary Risk Assessment." The number of zeroes and ½ LODs were adjusted accordingly to preserve the percent of detectable residues found in the original PDP data and to account for the % CT. These numbers were then added into the appropriate RDF. For partially blended food forms (PB), the PDP residue distribution was directly incorporated into the RDF with no decomposition. For blended food forms (B), the average residue from composite samples of PDP monitoring data was used as a single point estimate.

For the chronic and cancer dietary exposure analyses, a point estimate was used which was the average of the PDP monitoring data where the number of ½ LODs and zeroes were adjusted according to the average % CT reported by BEAD.

The Environmental Fate and Effects Division (EFED: Memo by Larry Liu and Richard Lee, D250088) has provided an analysis of available data and a screening level assessment using simulation models (GENEEC and SCI-GROW) to estimate the potential concentration of imazalil in ground and surface water. Imazalil is unlikely to contaminate surface and ground waters. Fate studies show that this chemical is immobile (average K_{oc} = 4,324 mL/g; average K_d = 130 mL/g) and is not expected to move offsite when used as a seed treatment. Both surface and ground water simulations (described later) showed that imazalil may reach drinking water supplies only at very low concentrations.

Occupational exposure scenarios can be described as short term (1-30 days) for seed treatment, intermediate term (30 days to several months) for citrus fruit handlers, and long term or chronic (>180 days/year) for chicken hatcheries.

HED has determined that there are potential exposures to mixers, loaders, applicators, or other handlers during usual use patterns associated with imazalil. Based on the use patterns and potential exposures described above, 13 major exposure scenarios are identified to represent the extent of imazalil uses: (1) mixing/loading liquid formulation for on-farm seed treatment, (2) mixing/loading liquid formulation for drenchers application, (3) mixing/loading liquid formulation to support waxing equipment, (4) mixing/loading the liquid formulation to support foaming equipment, (5) mixing/loading liquid formulation for high pressure handwand applications, (6) applying liquid formulation with a drencher, (7) applying liquid formulation in a foamer equipment, (8) applying liquid formulation in a waxing equipment, (9) applying liquid formulation with a high pressure handwand sprayer, (10) handler for commercial seed-treatment equipment, (11) apply/light smoke canisters, (12) mixing/loading and applying liquid with commercial seed-treatment equipment, (13) mixing/loading and applying seed treatment for on-farm seed treatment.

E. Risk Assessment/Characterization

Dietary. Imazalil acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model (DEEM™) software Version 7.75, which incorporates consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992.

In both acute and chronic risk assessments, exposure was compared to a population adjusted dose (PAD), which is the reference dose (RfD) reduced by the FQPA safety factor (10 or 3x). HED considers dietary residue contributions greater than 100% of the PAD to be of concern. The acute and chronic PADs (aPAD and cPAD) are 0.17 and 0.0025 mg/kg/day, respectively.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a point estimate of residue and summed to obtain a total daily pesticide exposure for a deterministic (Tier 1 or Tier 2) exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic (Tier 3/4) assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/food forms) and a per capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange-juice) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure.

Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

Estimated acute dietary risk is not of concern. Use of USDA Pesticide Data Program (PDP) monitoring data, and calculated livestock anticipated residues (ARs) results in a maximum dietary risk estimate of 15 % of the aPAD at the 99.9^{th} percentile for females of child bearing age (13-50 years old).

Estimated chronic dietary exposure is below HED's level of concern. Use of PDP monitoring data and calculated livestock ARs results in a maximum risk of 3 % of the chronic PAD for children 1-6, the most highly exposed population subgroup. Dietary risk for the general US population was estimated to be 1 % cPAD.

Estimated chronic dietary exposure for the general US population is 0.000034 mg/kg/day, based on use of PDP monitoring data and calculated livestock ARs. This exposure corresponds to a lifetime cancer risk estimate of 2.1×10^{-6} which exceeds HED's level of concern for cancer dietary exposure estimates of 1.0×10^{-6}. The Critical Commodity Contribution Analysis indicated that orange and grapefruit food forms were several of the major contributors to the cancer dietary risk estimate accounting for approximately $2/3^{rd}$ of the dietary exposure.

Drinking Water

Acute drinking water levels of concern (DWLOCs) were calculated based on the acute dietary (food) exposure, default body weights and water consumption figures. The acute DWLOC for females 13-50 years is 500 ppb. The estimated environmental concentrations (EECs) for surface water (GENEEC) and groundwater (SCI-GROW) were less than the acute DWLOC's, indicating that acute aggregate exposure to imazalil in food and water is less than HED's level of concern. The peak GENEEC EEC was 0.072 ppb, while the estimated groundwater EEC was negligible.

The EECs for surface water (GENEEC, 0.013 ppb) and groundwater (SCI-GROW, 0 ppb) were less than the chronic DWLOC (87 ppb for general population and 25 ppb for children 1-6 years), indicating that chronic exposure to imazalil in food and water is less than HED's level of concern.

Cancer DWLOCs were not calculated since the dietary cancer risk estimate exceeds the level of concern of 1×10^{-6}. It should be noted that EFED concluded that "imazalil is unlikely to contaminate surface and ground waters".

Occupational Risk Estimates

The results of the short-term dermal assessments (1-30 days assumed) for handlers in seed treatment facilities indicate that the all exposure scenarios provide MOEs greater than or equal to 100 at baseline attire (i.e., long pants, long sleeved shirts, no gloves). The results of the intermediate-term dermal assessments (100 days assumed) for for citrus handlers indicate that

the all exposure scenarios provide MOEs greater than or equal to 100 at baseline attire (i.e., long pants, long sleeved shirts, no gloves) except for mixing/loading liquid formulation for waxing equipment. The short, intermediate and long-term inhalation assessment indicates that the all exposure scenarios provide MOEs greater than or equal to 100 at baseline attire (i.e, no respirator). The intermediate-term dermal assessments (100 days assumed) for citrus handler indicate that the all exposure scenarios provide MOEs greater than or equal to 100 at PPE (i.e., long pants, long sleeved shirts, gloves). All the long-term dermal assessments (250 days assumed) for chicken hatchery handler indicate that the exposure scenarios provide MOEs greater than or equal to 100 at baseline**.**

No post-application dermal or inhalation risk assessment was performed for entry following smoke generator or spraying applications in chicken hatcheries. Based on the low vapor pressure and short half life (118 minutes) of imazalil following smoke generator or spraying applications in chicken hatcheries and subsequent ventilation for sufficient duration, post-application dermal or inhalation risk assessment for hatchery handlers was not required. Once appropriate ventilation has occurred, HED has no reason to believe that exposures to re-entering hatchery handlers would be harmful.

Due to the method of seed treatment HED has determined that soil-incorporated, post-application agricultural exposure is considered to be negligible as long as the soil is not directly contacted. However, farmers handling treated seed which has been stored for an indefinite time before use, may face a minimal exposure hazard. An estimate of the inherent risk from treated seed was conducted for descriptive purposes using relatively conservative assumptions. As there are no study data available on exposure to imazalil residue on treated seed, the exposure has been estimated using the unit exposure for handling granular formulations in PHED. The risk was found to be below the HED level of concern.

Non-Occupational (Residential) Exposure and Risk Assessment

There are no registered residential uses of imazalil and thus residential exposure is not expected.

Aggregate Risk Assessments

There are no registered residential uses of imazalil, so aggregation would include only food and water risk estimates.

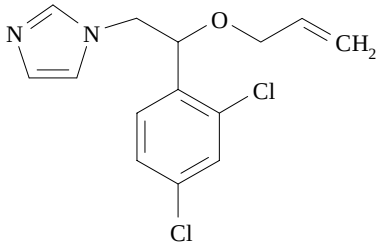
Acute aggregate risk estimates do not exceed HED's level of concern (aPAD of 0.017 mg/kg/day). The estimated environmental concentrations (EECs) for surface water (GENEEC) were less than the acute DWLOCs, indicating that acute aggregate exposure to imazalil in food and water is less than HED's level of concern. The acute DWLOC for Females 13-50 years is 500 ppb. The EECs for groundwater (SCI-GROW) were less than the acute DWLOC's, indicating that acute aggregate exposure to imazalil in food and water is less than HED's level of concern. The peak GENEEC EEC was 0.072 ppb, while the estimated groundwater EEC was negligible.

Chronic aggregate risk estimates do not exceed HED's level of concern. The EECs for surface water (GENEEC) were less than the chronic DWLOCs, indicating that chronic exposure to imazalil in food and water is less than HED's non-cancer level of concern. The EECs for groundwater (SCI-GROW) were less than the chronic DWLOC's, indicating that chronic exposure to imazalil in food and water is less than HED's level of concern.

An aggregate cancer assessment was not done because the cancer risk from food alone was estimated to be in excess $1x10^{-6}$.

II. PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

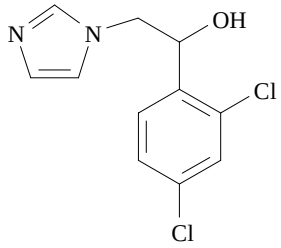
Imazalil [1-(2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl)-1*H*-imidazole] is a systemic fungicide registered for post-harvest treatment of citrus fruits and bananas (import use for bananas), for seed treatment of barley and wheat prior to planting and as a disinfectant in chicken hatcheries.



Imazalil: 1-[2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl]-1*H*-imidazole

MOLECULAR FORMULA:	$C_{14}\,H_{14}\,Cl_2\,N_2\,O$
MOLECULAR WEIGHT:	297.18
Reregistration Case Number:	2325
Chemical Number:	111901
CAS Registry No.:	35554-44-0
Melting point:	52.7°C
Vapor pressure (20°C):	$1.2x10^{-6}$ mm Hg
Water solubility (20°C):	180 - 293 ppm
Log K_{ow}:	3.82
Solubility:	very soluble in methanol, ethanol, 2-propanol, xylene, benzene, toluene, and solutions of mineral and organic acids. Soluble in n-heptane, hexane, and petroleum ether

Three metabolites of concern:



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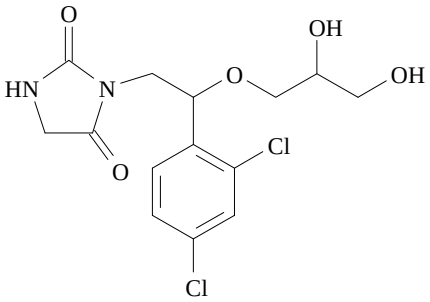

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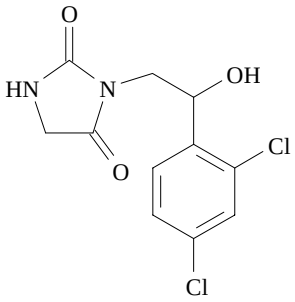

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A. R014821; FK411: 1-[2,4-dichlorophenyl)-2-(1*H*-imidazole-1-yl]-1-ethanol

B. R061000: 3-[2-(2,4-dichlorophenyl)-2-(2,3-dihydroxypropoxy)ethyl]-2,4-imidazolidinedione

C. R042449 **or** R043449: 3- **or** 2-(2-(2,4-dichlorophenyl)-2-(hydroxy)-2,4-imidazolidinedione

III. HAZARD ASSESSMENT

A. Toxicology Assessment

Imazalil is acutely toxic by the oral route (Category II) to rats [LD_{50} = 227-343 mg/kg; M+F], moderately toxic by the dermal route to rabbits (Category III) [$LD_{50} \geq 2000$ mg/kg; M+F rabbits]. Its inhalation toxicity is Category IV ($LC_{50} \geq 2$ mg/L). It is a severe eye irritant (Category I), but not a skin irritant (Category IV). It is not a skin sensitizer in animal testing. Acute toxic effects are lethargy, ptosis (drooping of the upper eyelids), decreased respiratory rate and gasping respiration, ataxia and death.

Imazalil (EC formulation) is absorbed by rat skin with an apparent 41% absorption (rounded to 40% in this assessment) of the applied dose within 10 hours of application. This dermal absorption factor was recommended by HIARC based on a dermal absorption study in rats (MRID No. 42913401) to be used to convert intermediate- and long-term exposures to equivalent oral doses. However, comparative oral and dermal toxicity studies suggest that the actual dermal absorption may be much less. For example, the maternal LOAEL in the submitted developmental rabbit study is 10 mg/kg/day at which severe maternal toxicity was seen. The dermal LOAEL in a range finding study for the 21-day dermal toxicity study in the rabbit was 250 mg/kg/day at which mild effects to the liver were observed. Based on these two studies, the apparent dermal absorption in the rabbit is approximately 4%.

Table 1: Acute Toxicity Values and Categories of Imazalil

Guideline Number and Study	RESULT	CATEGORY
870.1100 Acute Oral Toxicity - Rat	LD50=227 - 343 mg/kg	II
870.1200 Acute Dermal Toxicity - Rabbit	LD50 $\geq$ 2 g/kg	III
870.1300 Acute Inhalation Toxicity - Rat	LC50 $\geq$2.0 mg/L	IV
870.2400 Acute Eye Irritation	Irritating	I
870.2500 Acute Dermal Irritation - Rabbit	Non-irritating	IV
870.2600 Skin Sensitization Guinea Pig	Non-sensitizer	NA

The primary target organ for imazalil toxicity in animals is the liver. Enlarged livers were seen in rabbits after 6 days of dermal application at 250 mg/kg/day, increased liver weights and liver to body weight ratios, increased centrilobular swollen hepatocytes and increased vacuolization in hepatocytes after one month of dietary treatment at 32.1 mg/kg/day in rats, and similar histopathologic effects in mice at 38.6 mg/kg/day in the diet. In a chronic dietary rat study, there was an increased incidence of intra cytoplasmic inclusion bodies of hepatocytes, increased severity of hepatocyte vacuolization as well as bile duct proliferation at 15.5 mg/kg/day. Liver histopathologic lesions were also seen in a 23-month study in mice at 28.0 mg/kg/day. Increased liver vacuolization was also seen in male rats in a 2-generation reproduction study at 80 mg/kg/day. Increased liver weights were seen in dogs treated for one year at 20 mg/kg/day. The absolute and relative weight of thyroid glands was increased in male rats fed imazalil for two years at $\geq$65.8 mg/kg/day. Microscopic changes were also seen in the affected thyroids.

The data submitted to the Agency as well as those from the published literature do not demonstrate increased sensitivity of rats, mice, or rabbits from *in utero* exposure to imazalil. Developmental effects in fetuses occur at or above doses that cause maternal toxicity. Although there is no evidence of *in utero* susceptibility, there appears to be increased postnatal susceptibility of neonates to imazalil. In the 2-generation reproduction study, an increased susceptibility of the pups to imazalil was reported. Pup survival rate was adversely affected by imazalil treatment from birth to post natal day 4 in the F2 generation at the highest dose tested of 80 mg/kg/day. The HIARC determined that pup deaths resulted from an increased susceptibility to imazalil from the milk intake during lactation.

In carcinogenicity studies in rodents, imazalil was carcinogenic to male Swiss albino mice and male Wistar rats, based on significant increase in liver adenomas and combined adenomas/carcinomas. In rats there was also increased incidence of combined thyroid follicular cell adenomas/carcinomas. The HED CPRC (1994) and CARC (1998) classified imazalil as a Group C-carcinogen and recommended a linear low dose approach (Q_1^*) for quantification of human cancer risk. The CARC (1999) reclassified imazalil under the July 1999 Draft Guidelines for Carcinogenic Assessment in the category "Likely to be carcinogenic in humans". The Committee reaffirmed its earlier decision by recommending a linear low-dose (Q_1^*) extrapolation for quantification of human cancer risk. The most potent unit risk, Q_1^* for imazalil based on male mouse liver adenoma and/or carcinoma combined tumor rates is 6.1×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents (HED Doc 013842). Imazalil was non-mutagenic in both *in vivo* and *in vitro* mutagenicity assays.

The toxicology profile for imazalil is summarized in Table 2. The toxicology database required to support the reregistration of imazalil is complete except where noted. Acute and subchronic neurotoxicity and developmental neurotoxicity studies have been identified as data gaps

Table 2. Guideline Toxicology Studies for Imazalil

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rats	43965704(1996) Acceptable/non-guideline 0, 200, 400, 800 ppm M: 0, 16, 32, 64, mg/kg/d F: 0, 19, 38, 76 mg/kg/d	**NOAEL**: 200 ppm (15.8 and 18.7 mg/kg/day in ♂ and ♀, respectively. **LOAEL**: 400 ppm (32.1 and 37.9 mg/kg/day in ♂ and ♀, respectively), based on increased absolute and relative liver weights in ♂ and ♀ at 1 m, increased centrilobular swollen hepatocytes in ♂ at 1 m, slightly swollen adrenal cortical cells in ♀ at 3 m, possibly increased absolute and relative adrenal weights in females at 3 m, increased vacuolization in hepatocytes in ♀ at 1 m.
870.3100 90-Day oral toxicity rats	43965705(1996) Acceptable/non-guideline 0, 800,1600, 2400, 3200 ppm M: 0, 65, 129, 181, 252 mg/kg/d F: 0, 79, 150, 236, 333 mg/kg/d	**NOAEL**: <800 ppm (64.4 and 78.7 mg/kg/day in ♂ and ♀ , respectively). **LOAEL**: 800 ppm (64.4 and 78.7 mg/kg/day in ♂ and ♀ , respectively), based on possibly decreased bw and bw gains in ♂ and ♀, possibly decreased triglyceride and phosholipid in ♂, dark and more pronounced lobulation of livers in ♀, possibly increased relative liver/bw ratios in ♂, mild hepatocellular hypertrophy in ♂ and ♀, and mild 'fatty vacuolation' in the livers of ♀.
870.3100 90-Day oral toxicity mice	43222601 & 43292402 (1994) Acceptable/nonguideline 0, 50, 200, 600 ppm M: 0, 10, 39, 115 mg/kg/day F: 0, 11, 46, 138 mg/kg/day	**NOAEL** = 50 ppm (9.5 and 11.3 mg/kg/day in ♂ and ♀, respectively) **LOAEL** = 200 ppm (38.6 and 45.6 mg/kg/day in ♂ and ♀, respectively) based on increased incidence and severity of histopathologic effects, increased microsomal protein and increased microsomal cytochrome P450 content in the livers of both sexes.
870.3150 90-Day oral toxicity Dog	See one year study	See one year study
870.3200 21-Day dermal toxicity-Rabbit	42085201 (1991) 5/sex at 0, 10, 40 or 160 mg/kg/day 6-day range finding at 0, 63, 250 or 1000 mg/kg/day	**NOAEL** :160 mg/kg/day **LOAEL** : 250 mg/kg/day based on significant fissuring, scaling and swollen livers in the range finding study. No systemic toxicity was reported in main 21-day study.
870.3250 90-Day dermal toxicity	NA	NA
870.3465 90-Day inhalation toxicity	NA	NA
870.3700a Prenatal developmental in rodents-rats	41026603 (1988) Imazalil Sulfate technical: 0, 40, 80 or 120 mg/kg/day Acceptable/guideline	**Maternal NOAEL** = <40 mg/kg/day **LOAEL** = 40 mg/kg/day based on decreased food consumption **Developmental NOAEL** = 40 mg/kg/day **LOAEL** = 80 mg/kg/day based on decreased fetal weight

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700a Prenatal developmental in rodents-mouse	44578201 (1991) Imazalil Sulfate technical: 0, 10, 40, 80 or 120 mg/kg/day Acceptable/guideline	**Maternal NOAEL** = 10 mg/kg/day **LOAEL** = 40 mg/kg/day based on reduced bodyweight gains and corrected bodyweight gains **Developmental NOAEL** =80 mg/kg/day **LOAEL** =120 mg/kg/day based on increased resorption, postimplantation loss and reduced litter size
870.3700a Prenatal developmental in rodents-mouse	44567802 (1992) Imazalil Sulfate technical: 0, 10, 40, 80 or 120 mg/kg/day Acceptable/guideline	**Maternal NOAEL** = 10 mg/kg/day **LOAEL** = 40 mg/kg/day based on reduced bodyweight gains, corrected bodyweight gains and food consumption **Developmental NOAEL** = 10 mg/kg/day **LOAEL** = 40 mg/kg/day based on significant increase of fetuses and litters with extra 14th pair of ribs
870.3700b Prenatal developmental in nonrodents - rabbit	42593601 (1992) Imazalil Sulfate technical: 0, 5, 10 or 20 mg/kg/day Acceptable/guideline	**Maternal NOAEL** = 5 mg/kg/day **LOAEL** = 10 mg/kg/day based on decreased body weight and food consumption and increased mortality **Developmental NOAEL** = 5 mg/kg/day **LOAEL** = 10 mg/kg/day based on increased resorption and decreased number of fetuses.
870.3800 Reproduction and fertility effects 2-generation, rat	42570701 & 42949402 (1992) 0, 5, 20, 80 mg/kg/day Acceptable/guideline	**Parental/Systemic NOAEL** = 20 mg/kg/day **LOAEL** = 80 mg/kg/day based on decreased body weight gain (♂ & ♀) and increased liver vacuolation (♂). **Reproductive NOAEL** = 20 mg/kg/day **LOAEL** = 80 mg/kg/day based on increased duration of gestation. **Offspring NOAEL** = 20 mg/kg/day **LOAEL** = 80 mg/kg/day based on increased pup mortality from birth to day 4.
870.4100a Chronic toxicity rodents - rats	00162412 (1984) 18-Month study 0, 25, 100 or 400 ppm 47026101(1985) Chronic/Oncogenicity 0, 25, 100 or 400 ppm M: 0, 1, 3.7, 15.5 m/kg/d F: 1.2, 4.7, 20 mg/kg/day Unacceptable: not tested at adequate high dose	**NOAEL** = 3.7 mg/kg/day **LOAEL** = 15.5 mg/kg/day based on liver effects: increased incidence of intracytoplasmic inclusion bodies in hepatocytes, increased hepatocyte vacuolization and bile duct proliferation.
870.4100b Chronic toxicity dogs	41328802 (1989) 12-Month Chronic Oral Toxicity (Capsule) - 0, 1.25, 2.5, or 20 mg/kg/day Acceptable/guideline	**NOAEL** = 2.5 mg/kg/day **LOAEL** = 20 mg/kg/day, based on decreased body weight gain (♂ & ♀), increased alkaline phosphatase (♂ & ♀), increased liver weight (♂) and clinical symptoms of vomiting and soft stools.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4200 Carcinogenicity rats	44858001 (1999) Chronic/Oncogenicity 0, 50, 200, 1200, 2400 ppm M: 0, 2.7, 10.8, 65.8, 134.8 mg/kg/d F: 0, 3.6, 14.6, 85.2, 168.8 mg/kg/d Acceptable/guideline	**NOAEL** = 10.8 & 14.6 mg/kg/day in ♂ & ♀, respectively **LOAEL** = 65.8 & 85.2 mg/kg/day in ♂ & ♀, respectively based on reductions in body weight and weight gain and macro and micro-scopic effects in the liver of ♂ & ♀ rats and thyroid of ♂ rats. **Positive for liver and thyroid neoplasm in male rats.** Classified by HED CARC (1999) as **"Likely to be carcinogenic in humans" - with a Q_1^* of 6.11 x10^{-2} (mg/kg/day)$^{-1}$**
870.4300 Carcinogenicity mice	42972001 (1993) 23-Month Carcinogenicity in Mice 0, 50, 200 or 600 ppm M: 0, 6.8, 28, 88 mg/kg/d F: 0, 8.3, 35, 110 mg/kg/d	**NOAEL** = 50 ppm (6.8 mg/kg/day) in ♂; 200 ppm (110 mg/kg/day) in ♀ **LOAEL** = 200 ppm (28 mg/kg/day) in ♂ and 600 ppm (35 mg/kg/day) in ♀, based on increased liver histopathology **Positive for liver neoplasm in male mice.** Classified by HED CPRC (1994) and CARC (1998) as a **Group C - Possible human carcinogen - with a Q_1^* of 6.11 x10^{-2} (mg/kg/day)$^{-1}$**
Gene Mutation 870.5100	40729301(1988) Ames assay 5-500 µg/plate Acceptable/guideline	Negative in Salmonella strains up to toxic concentrations of 250-500 µg/plate with or without S-9 activation.
Cytogenetics 870.5375	40729302 (1986) HED 006818 Acceptable, pre 1991 guidelines	In an in vitro human lymphocytes chromosome aberration study, imazalil did not result in any increased chromosomal aberrations at concentrations ranging from 23 to 909 µg/ml culture
Other Effects 870.5300	43735003 (1988) Acceptable, pre 1991 guideline	In an in vitro cytogenetic study in mammalian cells (Chinese hamster V79 cells), imazalil, at doses ranging from 10 to 100 µg/ml, was not mutagenic both with and without activation
870.5395	00031599 (1979 HED Doc. 000057 Acceptable. Pre 1991 guideline	In a mutagenicity Micronucleus Test in rats, imazalil did not result in any increase in micronucleated polychromatic erythrocytes in any of the intraperitoneally doses tested (0, 20, 40 or 160 mg/kg
870.5500	43965702 (1996) Acceptable. 1991 guideline	In an in vivo/in vitro unscheduled DNA synthesis assays in mice administered single oral doses of imazalil of 125 or 250 mg/kg, imazalil was negative for genotoxicity but positive for cellular proliferation when tested at overtly toxic (250/ mg/kg; mortality 29/54) and cytotoxic doses
870.5500	43780201(1990) Acceptable pre 1991 guideline	In an unscheduled DNA synthesis (UDS) assay in rat hepatocytes imazalil at concentrations ranging from 0.09 to 9.0 µg/ml did not cause increased UDS.
870.6200a Acute neurotoxicity screening battery	DATA GAP	DATA GAP

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.6200b Subchronic neurotoxicity screening battery	DATA GAP	DATA GAP
870.6300 Developmental neurotoxicity	DATA GAP	DATA GAP
870.7485 Metabolism and pharmacokinetics	42012003 (1991) Metabolism C^{14} - Rat Single IV dose 1.25 mg/kg Single oral 1.25 mg/kg Single oral 20 mg/kg 14-day repeated oral 1.25 mg/kg Acceptable/guideline	^{14}C- Imazalil rapidly absorbed, distributed, metabolized and excreted in roughly equal amounts in urine and feces within 24 hours. Metabolized to more than 25 metabolites. Major metabolites identified. A metabolic pathway proposed. No significant bioaccumulation in tissues. No significant sex differences observed. No significant differences between dosing regiments.
870.7600 Dermal penetration	42913401 (1993) Dermal Absorption-Rats 0.004, 0.04, 0.4 or 4.0 mg/cm^2 Acceptable/guideline	Peak blood concentration at 1 hour for the 0.00- 0.4 mg/cm^2; at 10 hours for the 4.0 mg/cm^2. Percent absorption at 10 hours was 41%, 25%, 17% and 26% and at 24 hours was 48%, 39%, 31% and 29% of the applied doses of 0.004, 0.04, 0.4 or 4.0 mg/cm^2
Special studies	NA	NA

B. Dose Response Assessment

i. Determination of Susceptibility

The data submitted to the Agency as well as those from the published literature do not demonstrate increased sensitivity of rats, mice, or rabbits from *in utero* exposure to imazalil. Developmental effects in fetuses occur at or above doses that cause maternal toxicity. Although there is no evidence of *in utero* susceptibility, there appears to be increased postnatal susceptibility of neonates to imazalil. In the 2-generation reproduction study, an increased susceptibility of the pups to imazalil was reported. Pup survival rate was adversely affected by imazalil treatment from birth to post natal day 4 in the F2 generation at the highest dose tested of 80 mg/kg/day. The HIARC determined that pup deaths resulted from an increased susceptibility to imazalil from the milk intake during lactation.

The Health Effects Division (HED) FQPA Safety Factor Committee met on September 20, 1999 to evaluate the hazard and exposure data for imazalil and recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) be retained at 10x when assessing chronic dietary exposure and reduced to 3x for when assessing acute dietary exposure to this pesticide (HED No. 013762).

The FQPA SFC concluded that the FQPA safety factor is required because:

- The toxicology database for imazalil is incomplete (acute, subchronic, and developmental neurotoxicity studies are required);
- There is qualitative evidence of increased susceptibility following pre-/postnatal exposure to imazalil in the 2-generation reproduction study in rats (severe toxicity in neonates was seen in the presence of minimal maternal toxicity at the same dose).
- There is concern for neurobehavioral effects in offspring following prenatal exposure to imazalil which were reported in a published literature study conducted in mice (Tanaka 1995).

In its decision, the FQPA SFC determined that a factor of 3x was warranted for the assessment of both acute and chronic dietary risk because of the neurotoxicity data gap, i.e., the need for acute, subchronic, and developmental neurotoxicity studies in rats. The FQPA SFC also determined that a factor of 3x was warranted for the assessment of chronic dietary risk because of the susceptibility of neonates observed in the two-generation reproduction study in rats. As a consequence, the safety factor was retained at 10x for the assessment of chronic dietary risk and reduced from 10x to 3x for the assessment of acute dietary risk for females (13-50 years).

ii. Cancer Classification

The HED CPRC (1994) and CARC (1998) classified imazalil as a Group C-carcinogen and recommended a linear low dose approach (Q_1^*) for quantification of human cancer risk. The

CARC (1999) reclassified imazalil under the July 1999 Draft Guidelines for Carcinogenic Assessment in the category "Likely to be carcinogenic in humans". The Committee reaffirmed its earlier decision by recommending a linear low-dose (Q_1^*) extrapolation for quantification of human cancer risk. The most potent unit risk, Q_1^* for imazalil based on male mouse liver adenoma and/or carcinoma combined tumor rates is 6.1×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents (HED Doc 013842). Imazalil was non-mutagenic in both *in vivo* and *in vitro* mutagenicity assays.

iii. Toxicology Endpoint Selection

On June 15 and 22, 1999, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of imazalil, established an oral Reference Dose (RfD) for acute and chronic dietary risk assessments as well as dermal and inhalation endpoints for occupational risk assessments.

For acute dietary risk assessment, the NOAEL of 5 mg/kg/day from a developmental toxicity study in rabbits was chosen based on an increased incidence of resorption and decreased number of fetuses at the LOAEL of 10 mg/kg/day. The acute RfD was calculated using a 10x interspecies and 10x intraspecies uncertainty factor. The acute Population Adjusted Dose (aPAD) was 0.017 mg/kg/day (acute RfD 0.05 mg/kg/day ÷ 3x FQPA safety factor) and is applicable to Females 13-50 years only.

For chronic dietary risk assessments, the NOAEL of 2.5 mg/kg/day from a one year chronic feeding toxicity study in dogs was chosen based on systemic toxicity, decreased body weight gain, increased liver weight and increased alkaline phosphatase at the LOAEL of 20 mg/kg/day. The chronic Population Adjusted Dose (cPAD) was 0.0025 mg/kg/day (chronic RfD 0.025 mg/kg/day ÷ 10X FQPA safety factor).

To estimate short term dermal risks, a dermal NOAEL of 160 mg/kg/day was selected based on skin effects and swollen livers at the LOAEL of 250 mg/kg/day in a 21-day dermal study in rabbits. For estimating intermediate- and long- term dermal risks, dermal toxicity studies were not available and animal studies reflecting oral administration of the pesticide were used, along with a dermal absorption factor of 40%.

For intermediate-term dermal risk assessments, a NOAEL of 16 mg/kg/day was selected based on severe liver effects at the oral LOAEL of 32 mg/kg/day in a 90-day feeding study in rats. For long term dermal assessment, a NOAEL of 2.5 mg/kg/day was selected based on the oral LOAEL of 20 mg/kg/day in the one year study in dogs. HED believes that the resulting intermediate and long-term dermal endpoints are very conservative because based on comparative oral and dermal toxicity studies with imazalil, the dermal absorption factor appears to over predict the amount of imazalil available to elicit a toxic response.

For short-term inhalation risk assessment, a NOAEL of 5 mg/kg/day was selected based on the above developmental rabbit study. For intermediate and long-term inhalation risk assessment,

the NOAEL of 2.5 mg/kg/day was selected based on the one year dog study above.

For cancer risk estimation, the reader is referred to Section III.B.ii on cancr classificiaiton.

The dosages and toxicological endpoints proposed for various exposure scenarios are summarized in Table 3.

Table 3. The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE*
Acute Dietary Females 13-50 General Population: Not Relevant	NOAEL=5 UF = 100 FQPA SF = 3	Increased resorption and decreased number of fetuses at 10 mg/kg/day	Developmental-Rabbit Study	Not Relevant
	a PAD = Acute RfD/FQPA SF =0.05 mg/kg/day/3 = 0.017 mg/kg bw/day			
Chronic Dietary	NOAEL=2.5 UF= 100 FQPA SF = 10	Systemic toxicity: vomiting, soft stools, ↓body weight gain, ↑liver weight, ↑alkaline phosphatase at 20 mg/kg/day	Chronic Toxicity-Dogs	Not Relevant
	c PAD = Chronic RfD/FQPA SF =0.025 mg/kg/day/10 = 0.0025 mg/kg bw/day			
Dermal Absorption	41% based on a dermal absorption study in male rats			
Short-Term (Dermal)	Dermal NOAEL=160	Skin effects and swollen livers at 250 mg/kg/day	21 Day Dermal -Rabbit	100
Intermediate-Term (Dermal)[a]	Oral NOAEL=15.8	Severe liver effects at 32 mg/kg/day	Subchronic Study - Rats	100
Long-Term (Dermal)[a] (Non-cancer)	Oral NOAEL=2.5	Systemic toxicity: vomiting, soft stools, ↓body weight gain, ↑liver weight, ↑alkaline phosphatase at 20 mg/kg/day	Chronic Toxicity-Dogs	100
Cancer Chronic Dietary**	$\mathbf{Q_1^*}$ **=** 6.11×10^{-2} $(mg/kg/day)^{-1}$	Hepatocytic neoplasm	Carcinogenicity Study Mice	NA
Inhalation (Acute)	Not required: acute inhalation is category IV. Acute exposure not likely			
Inhalation (Short-term)	Oral NOAEL = 5	Increased resorption and decreased fetuses at 10 mg/kg/day	Developmental-Rabbit Study	
Inhalation (Intermediate and long term)	Oral NOAEL = 2.5	Systemic toxicity: vomiting, soft stools, ↓body weight gain, ↑liver weight, ↑alkaline phosphatase at 20 mg/kg/day	Chronic Toxicity-Dogs	

[a] = Since an oral value was selected, a 40% dermal absorption factor should be used for route to route extrapolation.

* MOEs are for occupational exposure risk assessments; there are no registered residential uses at the present time.
** For dermal Cancer risk assessment use 40% absorption factor.

iv. Endocrine Disruptor Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to

determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

Imazalil has been shown to induce thyroid tumors in male rats and liver tumors in male rats and male mice and was classified by CARC as “likely to be carcinogenic to humans”.

v. Incident Reports

The Agency has reviewed reported poisoning incidents associated with human exposure to imazalil. The Agency has consulted the following data bases for the poisoning incident data on the active ingredient imazalil: OPP Incident Data System - since 1992, Poison Control Data - 1993 through 1996, California Department of Pesticide Regulation Data - since 1982, and the National Pesticide Telecommunications Network (NPTN). One pesticide incident occurred in 1997 according to the Incident Data System, which resulted in minor symptoms. No cases of exposure were reported to Poison Control Centers for the time period 1993 through 1996. Detailed descriptions of 24 cases submitted to the California Pesticide Illness Surveillance Program (1982-1998) were reviewed. In 3 of these cases, imazalil was used alone or was judged to be responsible for the health effects. Only cases with a definite, probable or possible relationship were reviewed. In the first case, a lemon grader/sorter experienced a rash on her neck, face, and eyelids, which also itched. In the second case, a lemon grader/sorter, who was wearing gloves, wiped her face and experienced a rash. The physician was uncertain as to whether the patient had reacted to the chemical or a possible ringworm infection. In the third case, a worker was repairing a washer-waxer hose line when the product spilled onto his hands. He washed his hands for 15 minutes and experienced a rash on his hands the next day. On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, imazalil was not reported to be involved in human incidents.

IV. EXPOSURE AND RISK ASSESSMENT

A. Dietary Exposure (Food Sources)

i. Background

Imazalil [1-(2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl)-1*H*-imidazole] is a systemic fungicide registered for postharvest treatment of citrus fruits and bananas (foreign use on imported RAC only) and for seed treatment of barley and wheat prior to planting. Imazalil's end-use products are marketed in the United States under the trade names Fecundal® and Fungaflor®, both of which are emulsifiable concentrate (EC) formulations. Fungaflor® is also formulated as a soluble powder (SP) for use on bananas imported into the United States from Columbia, Costa Rica, Ecuador, Guatemala, Honduras, and Mexico. The reregistration of imazalil is being supported by Janssen Pharmaceutica, the basic producer.

Imazalil is a systemic fungicide used to prevent, treat and control diseases caused by a variety of pathogenic organisms (fungi), which include (but not limited to) *Aspergillus* in egg handling facilities and equipment, blue mold in citrus fruits and *Fusarium* in wheat and barley seeds.

According to the EPA OPP REFS label tracking system, there are 15 active labels (table 4), including two technical grade (98.50-98.94 percent active ingredient), one impregnated material (14.9 percent active ingredient), 4 liquids (up to 31 percent active ingredient), seven emulsifiable concentrates (up to 68.25 percent active ingredient), and a flowable concentrate (10 percent active ingredient). Impregnated material is used in smoke generators.

Table 4. Summary of Active Imazalil Products

PRODUCT NAME	% ACTIVE INGREDIENT	REG #/FORMULATION
VITAVAX EXTRA	2.00	400-438/IM
CLINAFARM EC	13.80	773-55/EC
CLINAFARM SMOKE GENERATOR	14.90	773-56/FC
DECCOZIL EC-279	68.25	2792-49/EC
DECCOZIL EC-289	22.20	2792-51/EC
NU-ZONE 10ME	10.00	2935-440/EC
GUSTAFSON FLO-PRO IMZ FLOWABLE	31.00	7501-127/ LIQUID
RTU-VITAVAX-EXTRA	1.20	7501-166/ LIQUID
MAGNATE TECHNICAL	98.50	11678-55/ TECHNICAL
FUNGAFLOR TECHNICAL	98.94	43813-2/ TECHNICAL
FUNGAFLOR 500 EC	44.60	43813-6/EC
FECUNDAL 100 EC	9.50	43813-14/EC
MAGNATE 500 EC	44.50	66222-20/EC
NU-ZONE 10ME	10.00	CA91001400/ LIQUID
GUSTAFSON FLO-PRO IMZ FLOWABLE	31.00	ID98001400/ LIQUID

ii. Sources of Imazalil Residues on Foods

At this time products containing imazalil are intended for occupational use only. No homeowner uses are referenced on any imazalil label reviewed. There are a number of commercial use patterns for imazalil. It is used in commercial and on farm seed treatment of wheat, barley and sudangrass. Of the quantity treated, 37% is done at commercial seed treatment facilities, and 63% is treated on farms. About 2% of the total wheat and barley acreage in the United States are treated with imazalil (use information provided by Janssen Pharmaceutica). Imazalil is also used in the hatchery equipment sanitation program. Hatchery equipment includes but is not limited to the empty hatchery, cabinets, setters, coolers, storerooms and handling equipment. A second use in hatcheries is for treatment of ventilation ducts to reduce the level of infectious organisms and spores. Imazalil is also used for preservation of citrus fruits after harvest. The percentage of the total fresh citrus crop treated with imazalil is estimated to be 62% (use information provided by Janssen Pharmaceutica).

For citrus, imazalil is used for post harvest treatment of fruit only. Citrus fruits for consumption are treated before being stored in the warehouses. The frequency of applications in hatcheries is difficult to determine since this depends on the sanitation protocol followed by the poultry facility. Some facilities clean the hatcher cabinets every day while others will only use imazalil once a week. It also depends on the number of hatcher cabinets in a facility. For seed treatment, seed will be treated as needed. However, it is industry practice only to treat enough seeds as are needed to be used that season.

iii. Imazalil Residues

The established tolerances for residues of imazalil in/on plant commodities [40 CFR §180.413(a)] are expressed in terms of the combined residues of imazalil and its metabolite R014821 [1-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-yl)-1-ethanol]. Plant commodity tolerances range from 0.05 ppm (barley grain, cottonseed, and wheat grain) to 10 ppm (citrus fruits). Tolerances are also established for the combined residues of imazalil and R014821 in citrus oil and citrus dried pulp, each at 25 ppm. The established tolerances for residues of imazalil in livestock commodities are expressed in terms of the combined residues of imazalil and its metabolites R014821 and R042243 [3-[1-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-yl)ethoxyl]-1,2-propanediol]. Livestock commodity tolerances range from 0.01 ppm (milk and fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep) to 0.50 ppm (liver of cattle, goats, hogs, horses, and sheep). No tolerances are established for residues in eggs or poultry tissues. The HED Metabolism Committee (L. Cheng, 8/30/94) concluded that in the absence of information to the contrary, any metabolite containing the 2,4-dichlorophenyl moeity is of toxicological concern, and must be included in the dietary risk assessment. The Committee also concluded that HED should define a list of metabolites containing this moiety which should be analyzed in livestock feeding studies and explicitly included in the tolerance expression. These metabolites together with the parent compound should serve as marker compounds which should, using the metabolite ratios found in the metabolism studies, be used to determine residue values for dietary risk assessment. The Committeee also concluded that residues of concern in plants include imazalil and its metabolite R014821.

Adequate GC/ECD methods are listed in the Pesticide Analytical Manual (PAM), Vol. II for enforcement of imazalil tolerances, as currently expressed. Codex MRLs for residues of imazalil in/on plant commodities are currently defined in terms of imazalil *per se*, and as such are not

compatible with U.S. tolerances.

Imazalil use in poultry hatcheries for control of *Aspergillus fumigatus* via a smoke generator has been considered to be a non-food use and HED has concluded that no tolerances need to be proposed as a result of this use when eggs are not present in the room being fumigated (see 773-EUP-R, memo of 8/12/85, A. Reiter and S. Hummel.) If eggs are present in the room during fumigation, then OPP considers this fumigation to be a food use. In this situation, residue data in poultry tissues and eggs will be required and tolerances on poultry and eggs will need to be proposed. A satisfactory pyrolysis study using carbon-14 imazalil to determine the composition of the smoke is required prior to the registration of the smoke application of imazalil.

B. Dietary Exposure Estimates

The Biological and Economic Analysis Division (OPP/BEAD) has provided usage information for imazalil (J. Alsadek, 11/5/01). PDP data (1994-1999) reflected analysis for imazalil only (i.e. metabolite residues were not quantified). HED used the PDP data which analyzed for imazalil only and adjusted the residues to account for the additional residues of concern. An adjustment factor was derived from nature of the residue studies in plants submitted by the registrant. Total radioactive residues were less than 0.004 ppm in the wheat metabolism study (L. Cheng, D187506, 1/5/94); therefore, wheat PDP data for parent were used without adjusting for metabolites. Total radioactive residues were less than 0.003 ppm in banana pulp from the banana metabolism study (L. Cheng, D224876, 6/11/96); therefore, banana PDP data for parent were used without adjusting for metabolites. A factor of 1.4 to convert the orange PDP data to account for metabolite R014821 residues in orange pulp was calculated from the nature of the residue study in oranges (L. Cheng, D198235, 4/28/94). The orange pulp TRR data was used since PDP peels the orange samples before analysis. PDP samples of milk were analyzed for imazalil only and showed no detectable residues of parent in 692 samples. Imazalil and residues of the marker metabolites were all <0.06 ppm (LOQ) in milk in the metabolism study (F. Suhre, D182706, 2/16/93). Total imazalil residues after adjusting for marker metabolite concentrations were less than the reported LOQ of 0.06 ppm (0.02 ppm for each compound) in the 5x feeding level of the ruminant feeding study (S. Piper, D245510, 1/22/99) when normalized to the 1X feeding level. Therefore, milk food forms were considered to be negligible or zero, and were excluded from the dietary exposure analysis. For anticipated residues using PDP data, half the Limit of Detection (LOD) value was a weighted average of all laboratory LODs. Bananas had PDP monitoring data which contained over-tolerance residues. These values were removed in the undecomposited residue distribution file (per HED Dietary Exposure Science Advisory Council policy) since no clear pattern of over-tolerance residues was occurring. In addition, when decompositing the PDP data for bananas over-tolerance values were generated. In accordance with HED policy, these over-tolerance values were "set back" to the tolerance of 0.2 ppm.

For non-blended food forms (NB), single unit residue values were included in the residue distribution file (RDF) for the acute analysis; these single unit residues were statistically generated by way of decomposition of composite PDP residue values using the method described in the H. Allender paper (5/26/99) titled "Statistical Methods for Use of Composite Data in Acute Dietary Risk Assessment." The number of zeroes and ½ LODs were adjusted accordingly to preserve the percent of detectable residues found in the original PDP data and to account for

the % CT. These numbers were then added into the appropriate RDF. For partially blended food forms (PB), the PDP residue distribution was directly incorporated into the RDF with no decomposition. For blended food forms (B), the average residue from composite samples of PDP monitoring data was used as a single point estimate.

For the chronic dietary exposure analyses, a point estimate was used which was the average of the PDP monitoring data where the number of ½ LODs and zeroes were adjusted according to the average % CT reported by BEAD.

Codex Harmonization

The Codex Alimentarius Commission has established several maximum residue limits (MRLs) for imazalil in/on various raw agricultural commodities. The Codex MRLs are expressed in terms of imazalil *per se*. The Codex MRLs and the U.S. tolerances are incompatible with respect to tolerance expression. The U.S. tolerances for plant commodities are expressed in terms of the combined residues of imazalil and its metabolite R014821. The expression of U.S. tolerances for livestock commodities listed under 40 CFR §180.413(a) should be amended to regulate imazalil, 3-[2-(2,4 dichlorophenyl)-2-(2,3- dihyroxypropxy)ethyl]-2,4-imidazolidinedione (FK772), and 3-[2-(2,4 dichlorophenyl)-2-(hyroxy)]-2,4-imidazolidinedione (FK284). Both Codex and U.S. have established MRLs/tolerances for bananas, citrus fruits, and wheat grain, forage, hay, and straw. However, the residue levels are not in harmony presumably because of differences in good agricultural practices. A numerical comparison of the Codex MRLs and the corresponding reassessed U.S. tolerances is presented in Table 5.

C. Dietary Risk Estimates (Food Sources)

HED conducts dietary risk assessments using the Dietary Exposure Evaluation Model (DEEM™), which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, the entire distribution of single day food consumption events is combined with either a single residue level (deteministic analysis, risk at 95th percentile of exposure reported) or a distribution of residues (probabilistic analysis, referred to as "Monte Carlo," risk at 99.9th percentile of exposure reported) to obtain a distribution of exposure in mg/kg/day. For chronic dietary risk assessments, the three-day average of consumption for each sub-population is combined with residues in commodities to determine average exposure in mg/kg/day.

Table 5. Codex MRLs for Imazalil and applicable U.S. tolerances

Codex			Reassessed U.S. Tolerance (ppm)	Recommendation and Comments
Commodity (As Defined)	MRL (mg/kg)	Step		
Banana	2 Po [a]	CXL	3.0	
Citrus fruits	5 Po	CXL	10.0	
Cucumber	0.5	CXL		No U.S. registration.
Gherkin	0.5	CXL		No U.S. registration.
Melons, except watermelon	2	CXL		No U.S. registration.
Persimmon, Japanese	2 Po	CXL		No U.S. registration.
Pome fruits	5 Po	CXL		No U.S. registration.
Potato	5 Po [b]	CXL		No U.S. registration.
Raspberries, Red, Black	2	CXL		No U.S. registration.
Strawberry	2	CXL		No U.S. registration.
Wheat	0.01(*)[c]	CXL	0.1 for grain	
Wheat straw and fodder, Dry	0.1	CXL	0.5 for forage, hay, and straw	

[a] Po = Postharvest treatment of the commodity.
[b] Washed before analysis.
[c] Asterisk designates MRL set at the limit of quantitation.

i. Acute Dietary Risk Estimates

Only acute dietary risk assessment for females 13 - 50 is required. Estimated acute dietary exposure for this subpopulation is below HED's level of concern (Table 6 & 7). Use of PDP monitoring data, field trial data, and calculated livestock ARs results in a risk estimate of 15 % of the acute PAD at the 99.9th percentile for the female subpopulation. The most significant contributors to the exposure were grapefruit-peeled (~34%), and oranges-peeled (~59%which were each represented by USDA/PDP monitoring data through reported residue values.

Table 6. Summary of Dietary Risks.

Risk Type	**Residue Type and Population**		**Exposure (mg/kg/day)**	**% PAD, or cancer risk**
Chronic	Anticipated Residue Contribution	U.S. Population	0.000034	1% of cPAD
		Children 1-6	0.000069	3% of cPAD
Cancer[1]	Average Anticipated Residues	U.S. Population	0.00003	2.1×10^{-6}
Acute	Anticipated Residue Distributions	Females 13-50 (99.9th percentile)	0.002503	15% aPAD

[1] Based on the Q_1^* of 6.11×10^{-2} $(mg/kg/day)^{-1}$
aPAD = 0.017 mg/kg/day; cPAD = 0.0025 mg/kg/day

Table 7: Acute dietary exposure (mg/kg bw/day) and risk (%aPAD) for imazalil from the RACs and seed treatments that are registered for imazalil.

Subgroups	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	%aPAD	Exposure	%aPAD	Exposure	%aPAD
Females 13-50	0.000070	<1	0.0049	3	0.002503	15

ii. Chronic Dietary Risk Estimates

Estimated chronic dietary exposure is below HED's level of concern (Table 8). Use of PDP monitoring data and calculated livestock ARs results in a maximum risk of 3 % of the chronic PAD (% cPAD) for children 1-6. Dietary risk for the general US population was estimated to be 1 % cPAD.

Bananas, citrus fruits and meat are the contributors to the imazalil exposure. Each of these commodities' residues are represented by USDA/PDP monitoring data.

Table 8. Imazalil Chronic Dietary Exposure Risk

Subgroup	Exposure mg/kg bw/day	Percent of cPAD
U.S. Population (Total)	0.000034	1%
All infants (< 1 year)	0.000028	1%
Children 1-6 yrs	0.000069	3%
Children 7-12 yrs	0.000048	2%

iii. Cancer Dietary Risk Assessment

Estimated chronic dietary exposure for the general US population is 0.000034 mg/kg/day, based on use of PDP monitoring data and calculated livestock ARs; this exposure corresponds to a lifetime cancer risk estimate of 2.1×10^{-6} for the general US population Table 9). HED's level of concern for cancer dietary exposure estimates is 1.0×10^{-6}; therefore, the estimated cancer risk associated with the use of imazalil exceeds HED's level of concern for the general US population at 2.1×10^{-6}. The Critical Commodity Contribution Analysis indicated that orange and grapefruit food forms were several of the major contributors to the cancer dietary risk estimate accounting for approximately 2/3 of the dietary exposure. In order to understand the impact of assumptions at the exposure estimate, a sensitivity analysis was performed inserting zeroes in place of the ½ LODs for bananas; this resulted in an estimated cancer dietary exposure of 0.000032 mg/kg/day and a lifetime cancer risk estimate of 1.9×10^{-6} for the general US population. Another sensitivity analysis was performed by inserting zero residue values for meat and fat, along with the zeroes in place of the ½ LODs for bananas; this resulted in an estimated cancer dietary exposure of 0.000029 mg/kg/day and a lifetime cancer risk estimate of 1.8×10^{-6} for the general US population. These sensitivity analyses support the conclusion that the estimated cancer risk is largely due to imazalil residues in citrus commodities.

Table 9. Imazalil Cancer Dietary Exposure Risk

Population Subgroup)	Exposure mg/kg/day	Lifetime Risk, Q* = 0.0611
U.S. Population	0.000034	2.1E-06

D. Uncertainties in Dietary Exposure Assessment

The analytical method used by USDA in data collection analyzes for imazalil *per se*; therefore, an adjustment factor of 1.4 (for the metabolite R014821 was derived from the nature of residue study in oranges. This adjustment factor was translated to all citrus. Percent crop treated data were used for bananas, citrus juices, and livestock tissues. The BEAD reported % CT data for citrus was less than the percent detectable residues in the PDP data, therefore, the PDP data were used "as is" to demonstrate the worst case scenario. There were three detects in the PDP banana data which were over the tolerance. These values were removed in the undecomposited residue distribution file (per HED Dietary Exposure Science Advisory Council policy) since no clear pattern of over-tolerance residues was occurring. Decompositing yielded a number of over-tolerance values in the residue distribution file. These over-tolerance values were "set back" to the tolerance values per HED policy. PDP data for oranges were translated to lemon, lime, grapefruit, tangelo, and tangerine. PDP data for orange juice were translated to all citrus and adjusted for % CT for the respective commodity. PDP data for banana were translated to plantain. PDP data for wheat were translated to barley. PDP analyzed 692 milk samples for imazalil in 1996, 1997, and 1998. No detectable imazalil residues were found. Total imazalil residues after adjusting for marker metabolite concentrations were less than the reported LOQ of 0.06 ppm (0.02 ppm for each compound) in the 5x feeding level of the ruminant feeding study when normalized to the 1x feeding level. Therefore, milk food forms were considered to be negligible or zero, and were excluded from the dietary exposure analysis.

The dietary exposure analyses is a highly refined Tier 3 assessment since % CT and PDP monitoring data were used in the analyses. The Critical Commodity Contribution Analysis indicated that orange and grapefruit food forms were several of the major contributors to the cancer dietary risk estimate accounting for approximately 2/3 of the cancer dietary exposure. Due to the post-harvest use on citrus no significant decline of imazalil residues (beyond washing and peeling done by PDP prior to analysis) is not expected.

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys, (e.g., nursing and non-nursing infants or Hispanic females). Therefore, risks estimated for these population subgroups were included in representative populations having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years).

E. Drinking Water Exposure

The Environmental Fate and Effects Division (EFED: Memo by Larry Liu and Richard Lee, D250088) has provided an analysis of available data and a screening level assessment using simulation models to estimate the potential concentration of imazalil in ground and surface water. Imazalil is unlikely to contaminate surface and ground waters. Fate studies show that this chemical is immobile (average K_{oc} = 4,324 mL/g; average K_d = 130 mL/g) and is not expected to move offsite when used as a seed treatment. Both surface and ground water simulations

(described below) show that imazalil may reach drinking water supplies only at very low concentrations.

i. Surface Water

Surface water concentrations of imazalil were estimated with GENEEC using current EFED guidance (one application/year at 0.01 lb ai/acre, aerobic soil metabolism $t_{1/2}$ = 166 days and a minimum K_{oc} of 2,081 mL/g). The peak concentration predicted by GENEEC is 0.072 ppb, while the 56-day average value is 0.037 ppb (Table 10).

ii. Ground Water

Ground water concentrations were predicted with SCI-GROW according to EFED current guidelines (one application/year at 0.01 lb ai/acre, aerobic soil metabolism $t_{1/2}$ = 166 days and a median K_{oc} of 4,026 mL/g). The predicted groundwater concentration is negligible (0.0002 ppb).

F. Drinking Water Risk Estimates

EFED has recommended that the Health Effects Division use the concentrations presented in Table 10 for drinking water EECs.

Table 10. Drinking water estimated environmental concentrations for imazalil.

Model	EEC's
Surface Water (GENEEC) Chronic Non-Cancer Exposure	Peak = 0.072 ppb Average 56 day = 0.037 ppb*
Groundwater (SCI-GROW)	Negligible

* Current HED policy states that the average 56 day GENEEC value should br divided by 3 for chronic DWLOC calculation

GENEEC is not an ideal tool for drinking water exposure assessments. Surface-water-derived drinking water tends to come from bodies of water that, are substantially larger than a 1-hectare pond. Furthermore, GENEEC assumes that essentially the whole basin receives an application of the chemical. In virtually all cases, basins large enough to support a drinking water facility will contain a substantial fraction of area that does not receive the chemical. Furthermore, there is always at least some flow (in a river) or turn over (in a reservoir or a lake) of the water so the persistence of the chemical near the drinking water facility is usually overestimated by GENEEC. Given all this, GENEEC does provide an upper bound on the concentration of the pesticide that could be found in drinking water and therefore can be appropriately used in screening calculations.

i. DWLOC's for Chronic Risk Assessment

Chronic DWLOCs were calculated based on the chronic dietary (food) exposure and standard body weights and water consumption figures (Table 11). The Agency's standard body weights

and water consumption values used to calculate DWLOCs are as follows: 70kg/2L/day (adult male), 60 kg/2L/day (adult female), and 10 kg/L/day (child). To calculate the chronic DWLOC, the chronic dietary food exposure was subtracted from the chronic PAD using the equation:

$$DWLOC_{chronic}\ (\mu g/L) = \frac{[\text{chronic water exposure (mg/kg/day) x body weight(kg)}]}{[\text{consumption (L/day) x } 10^{-3}\ \text{mg/}\mu g]}$$

Where chronic water exposure (mg/kg/day) = [cPAD - chronic food (mg/kg/day)].

Table 11. DWLOC for chronic exposure to imazalil

Population Subgroup	Chronic PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure (mg/kg/day)	$DWLOC_{chronic}$ (µg/L)	GENEEC (µg/L)	SCI-GROW (µg/L)
US Population	0.0025	0.000018	0.00248	87	0.013	0
Children 1-6	0.0025	0.000036	0.00246	25	0.013	0

ii. DWLOC's for Acute Exposure

Acute DWLOCs were calculated based on the acute dietary (food) exposure and standard body weights and water consumption figures (Table 12). The Agency's standard body weights and water consumption values used to calculate DWLOCs are as follows: 70kg/2L/day (adult male), 60 kg/2L/day (adult female), and 10 kg/L/day (child). To calculate the acute DWLOC, the acute dietary food exposure was subtracted from the acute PAD using the equation:

$$DWLOC_{acute}\ (\mu g/L) = \frac{[\text{acute water exposure (mg/kg/day) x body weight(kg)}]}{[\text{consumption (L/day) x } 10^{-3}\ \text{mg/}\mu g]}$$

Where acute water exposure (mg/kg/day) = [aPAD - acute food (mg/kg/day)].

iii. DWLOC's for Cancer Risk Assessment

Cancer DWLOCs were not calculated since cancer risk from food alone is 2.1×10^{-6}. Any dietary contribution from drinking water would result in risks exceeding 2.1×10^{-6}. It should be noted that EFED concluded that "imazalil is unlikely to contaminate surface and ground waters".

Table 12. Acute Exposure and DWLOC.

Population Subgroup	Acute PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Water Exposure (mg/kg/day)	$DWLOC_{acute}$ (µg/L)	GENEEC (µg/L)	SCI-GROW (µg/L)
Females 13-50	0.017	0.001903	0.015097	500	0.072	0

iv. Non-Dietary Exposure

At this time, products containing imazalil are intended for commercial use only. No homeowner uses are referenced on any imazalil labels reviewed. It is used in commercial and on farm seed treatment of wheat, barley and sudangrass. Of the quantity treated, 37% was done at commercial seed treatment facilities, and 63% was treated on the farm. About 2% of the total wheat and barley acreage in the United States are treated with imazalil. Imazalil is also used in the hatchery equipment sanitation program. Hatchery equipment includes but is not limited to the empty hatchery, cabinets, setters, coolers, storerooms and handling equipment. A second use in hatcheries is for treatment of ventilation ducts to reduce the level of infectious organisms and spores. Imazalil is also used for preservation of citrus fruits after harvest. The percentage of the total fresh citrus crop treated with imazalil is estimated to be 62%.

G. Occupational Exposure and Risk Estimates

HED has determined that there are potential exposures to mixers, loaders, applicators, or other handlers during usual use-patterns associated with imazalil. Based on the use patterns and potential exposures described above, 13 major exposure scenarios are identified to represent the extent of imazalil uses.

Exposure scenarios include: (1) mixing/loading liquid formulation for on- farm seed treatment, (2) mixing/loading liquid formulation for drenchers application, (3) mixing/loading liquid formulation to support waxing equipment, (4) mixing/loading the liquid formulation to support foaming equipment, (5) mixing/loading liquid formulation for high pressure handwand applications, (6) applying liquid formulation with a drencher, (7) applying liquid formulation in a foamer equipment, (8) applying liquid formulation in a waxing equipment, (9) applying liquid formulation with a high pressure handwand sprayer, (10) handler for commercial seed-treatment equipment, (11) apply/light smoke canisters, (12) mixing/loading and applying liquid with commercial seed-treatment equipment, (13) mixing/loading and applying seed treatment for on-farm seed treatment.

i. Occupational Handler Exposure Data Sources and Assumptions

Mixer/loader/applicator exposure data for imazalil were required since one or more toxicological criteria had been triggered. Requirements for applicator exposure studies are addressed by Series 875 Group A (formerly Subdivision U of the Pesticide Assessment Guidelines). One handler exposure study and one air monitoring study were submitted by the registrant and are summarized below.

MRID No. - 447315-01. Review of assessment of worker exposure to Commercial Seed Treatment in Seed Treating Plants (Vitavax® 3RS flowable- Canola-Alberta, Canada). Workers were monitored for dermal and inhalation exposure during the loading, application, bagging, sewing, and stacking of Canola seeds treated with Vitavax ® RS Flowable.
The test substance is a water-based flowable seed treatment formulation containing three active ingredient, Lindane (48.7%), Thiram (6.43 %), and Carbathin (3.34%). UniRoyal had submitted this surrogate worker exposure study in support of the reregistration process for imazalil.

This study was conducted at three seed-treatment plants in Ontario, Canada. The three facilities were representative of large, medium and small seed-treating operations and all sites used different seed treatment equipment. A total of nine replicates were included in the study. The guidelines suggests that at least 15 replicates be examined per study. Four of the replicates were categorized as loader/applicators and the remaining five workers were categorized as seed handlers. The sampling period consisted of one 8 hour work day. The maximum application rate for seed treatment of approximately 562 ml (19 oz) of formulated product per 25 kg (55.31lb) seed was applied at each site. Treated seed samples were collected twice at each test site to verify the actual application rate. The study is only partially compliant with OPPTS 875 Group A test guidelines.

The geometric mean values obtained from this study had the lowest standard deviation and are presented in Table13.

Table 13 : Summary of the Exposure values of Canola Commercial Seed Treatment to Lindane in Canada

Scenario	mg/lb ai (no gloves)	mg/lb ai (gloves)
Loader/Applicator (Dermal)	0.36	0.063
Seed Handler (Dermal)	0.015	0.0022
Loader/Applicator (Inhalation)	0.0014	0.0014
Seed Handler (Inhalation)	0.00018	0.00018

On-farm seed treatment is considered to be 63% of the total use of treated seed in the U.S.(use information provided by Janssen Pharmaceutica). The only applicable study available to HED was conducted by Fenske, et al., 1990 and published in Arch. Environmental Contamination and Toxicology, vol. 19. Dermal and respiratory exposures of 4 workers during the manual treatment of winter wheat at a commercial wheat farm in South Dakota. A dust formulation containing 18.75 percent lindane, packed in 10 lb bags was applied at the label rate of 2 ounces per bushel of seed. The seed and formulation were mixed with a stick. The rest of the grain is then added and the procedure repeated. The dermal exposure estimated by Fenske, was 10.4 mg/lb ai and inhalation exposure estimate 2.4 µg/lb ai. Dust formulation by far has a higher potential for exposure than the imazalil emulsifiable concentrate formulations. Since this study was the only source of data available to HED for assessing on farm seed treatment therefore, it was used as a screening level to make an estimation on the risk involved.

MRID No. - 426034-01. The Assessment of Aerial Levels of imazalil (R 23 979) Resulting from Smoke Generator Applications - Volume II - Reentry Protection (Inhalation Exposure). The study does not appear to have been conducted in accordance with a specific guideline or data

requirement, but was submitted in support of reregistration of the pesticide product Clinafarm Smoke Generator®.

The study was conducted in a 33 m^3 experimental room. Five smoke generators were ignited and air concentrations were sampled using impingers at intervals from 30 minutes to 24 hours after release. The application rate used in this study was nearly double the recommended rate: 25 grams per 33 m^3, or 0.758 g/m^3. To sample the air in the experimental room, a glass tube 3 m long with an 8 mm internal diameter (I.D.) was extended into the center of the room. The air in the experimental room was sampled three times at each of five intervals, starting at 30 minutes after smoke generation began (i.e., 0.5h, 2.5h, 4.5h, 6.5h, and 8.5h). An additional sample was collected at 24 hours after initial time (i.e., t = 24h). Each of the three samples in a sampling set were collected sequentially (i.e. for 10 minutes, 10 minutes and 20 minutes - making 40 minutes in all). Each was also collected at different air-flow rates. A half-life of 118 minutes was calculated from this study. No laboratory recovery, fortified sample recovery, or blank analytical data were presented. No sample chromatograms or standard curve data were available for review. This study is not a true field exposure study. However only portion of the Group B: Postapplication Exposure Monitoring Test Guidelines, 875.2500, Inhalation Exposure Guideline, Small Scale Environmental Chambers does apply to this type of study.

Table 14 presents the exposure scenarios, application rates and amount potentially treated that have been used in the exposure calculations. Imazalil labels include a multitude of uses and a wide range of application rates. Therefore, the rates presented are not all inclusive and an attempt has been made to assess a range of application rates to ensure that all use rates and exposure scenarios are represented.

The above seed treatment exposure data are used to assess the potential handler exposure to imazalil while conducting similar seed treatment activities. PHED V1.1 (1998) has also been used to assess the exposure scenarios which were not monitored by the registrant, however there are a few scenarios that could not be assessed due to a data gap. While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration,, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. PHED was designed by a Task Force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates).

Users select criteria to subset the PHED database to reflect the exposure scenario being evaluated. The subsetting algorithms in PHED are based on the central assumption that the magnitude of handler exposures to pesticides are primarily a function of activity (e.g., mixing/loading, applying), formulation type (e.g., wettable powders, granulars), application method (e.g., aerial, groundboom), and clothing scenarios (e.g., gloves, double layer clothing). Once the data for a given exposure scenario has been selected, the data are normalized (i.e., divided by) by the amount of pesticide handled resulting in standard unit exposures (milligrams of exposure per pound of active ingredient handled). Following normalization, the data are

statistically summarized. The distribution of exposure values for each body part (e.g., chest, upper arm) is categorized as normal, log normal, or "other" (i.e., neither normal nor log normal). A central tendency value is then selected from the distribution of the exposure values for each body part. These values are the arithmetic mean for normal distributions, the geometric mean for lognormal distributions, and the median for all "other" distributions. Once selected, the central tendency values for each body part are composited into a "best fit" exposure value representing the entire body.

The handler exposure assessments encompass all of the major uses of imazalil throughout the country. The assumptions and uncertainties are identified below to be used in risk management decisions:

Application Rates: The application rates are the maximum allowable that were identified on the available product labels. The citrus drencher maximum application rate is assessed at 0.6255 lb/100 gal and wax treatment and foamer at 1.665 lb/100 gal. The seed treatment maximum application rates are 0.006719 lb ai/100 lb for sudangrass, 0.003906 lb ai/100 lb for wheat and barley (mist type seed treater) and 0.01008 lb ai/100 lb for slurry-type seed treater. The egg handling facilities (hatchery and equipment) 0.00032 lb/1000ft^3 for spray and 0.022 lb/1000ft^3 for smoke generator when needed.

Amount Handled: The daily number of gallons mixed for a drencher is assumed to be 1,200 (1,080,000 lbs of citrus) and wax treatment is assumed to be 1,600 (1,440,000 lbs of citrus) gallons per day. For hatcheries the average size of setters 2,520 cubic feet and hatchers 288 cubic feet. A typical hatchery consists of 15 hatchers and 15 setters. For seed treatment Gustafson's seed treaters handle a minimum of 7.5 metric tons/hr to 40.8 metric tons/hr (capacity is based on wheat). For on-farm treatment it was assumed that 100 acres (120 lbs/acre) of wheat and barley can be planted in a day.

Unit Exposures: The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has developed a set of grading criteria to characterize the quality of the original study data. The assessment of data quality is based on the number of observations and the available quality control data. While data from PHED provides the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases

Data Gap: No exposure studies were provided by the registrant for drencher, waxing equipment, foaming equipment or smoke generator. For drencher and waxing equipment only a liquid mixer loader scenario was assessed. For smoke generator air concentration was calculated based on maximum application rate at baseline and PPE. For on-farm seed treatment, a published study from Fenske, was used. Dust formulation by far has a higher potential for exposure than the imazalil emulsifiable concentrate formulations. Since this study was the only source of data available to HED for assessing on farm seed treatment, therefore it was used as a screening level to make an estimation on the risk involved.

Table 14: Exposure Variables for Uses of Imazalil

Exposure Scenario (Scenario #)	Are Chemical Specific Monitoring Data Available?[a]	Are PHED Data Available?	Application Rates (lb ai/1000ft^3)[b] (lb ai/100 gallons)[b] (lb ai/100 lb)[b]	Daily lb or ft^3 Treated[c]	Daily Gallon Treated[d]
Mixer/Loader Exposure					
(1) mixing/loading liquid formulation for on-farm seed treatment	No	Yes	min 0.003906 lb (0.5 oz) ai/100lb for wheat and barley	12,000	Not Available
			max 0.01b (1.5 oz) ai/100lb for wheat and barley		
(2) mixing/loading liquid formulation for drenchers applications	No	Yes	0.6255 lb ai/100 gallons	1,080,000 lbs	1,200
(3)mixing/loading liquid formulation for waxing equipment	No	Yes	1.665 lb ai/ 100 gallons	1,440,000 lbs	1,600
(4) mixing/loading liquid formulation for foaming equipment	No	Yes	1.665 lb ai/ 100 gallons	Not Available	Not Available
(5) mixing/loading liquid formulation for high pressure hand wand applications	No	Yes	0.00032lb ai/1000ft^3 chicken hatcheries	37800ft^3 setters and 4320ft^3 hatchers	Not available
Applicator					
(6) applying liquid formulation with a drencher	No	No	0.6255 lb ai/100 gallons assumed 1 gal per 900 lbs	1,080,000 lbs	1,200
(7) applying liquid formulation for a foamer equipment	No	No	1.665 lb ai/ 100 gallons	Not Available	Not Available
(8) applying liquid formulation for a waxing equipment	No	No	1.665 lb ai/ 100 gallons	1,440,000 lbs	1,600
(9) applying liquid formulation with a high pressure handwand sprayer	No	Yes	0.00032lb ai/1000ft^3 chicken hatcheries (½ oz per 150ft^3)	37800ft^3 setters and 4320ft^3 hatchers	Not Available
(10) handler for commercial seed-treatment equipment	No Surrogate data used MRID #447315-01	No	0.006719lb ai/100 lb for Sudangrass (1 oz)	min 132,000 lbs (commercial)	Not Available
				max 718,000 lbs (commercial)	
			min 0.003906 lb (0.5oz) ai/100lb for wheat and barley	min 132,000 lbs (commercial)	
				max 718,000 lbs (commercial)	
			max 0.01b (1.5 oz) ai/100lb for wheat and barley	min 132,000 lbs (commercial)	

Exposure Scenario (Scenario #)	Are Chemical Specific Monitoring Data Available?[a]	Are PHED Data Available?	Application Rates (lb ai/1000ft^3)[b] (lb ai/100 gallons)[b] (lb ai/100 lb)[b]	Daily lb or ft^3 Treated[c]	Daily Gallon Treated[d]
				max 718,000 lbs (commercial)	
11) apply/light smoke canisters	No only an air monitoring study available MRID # 426034-01	No	0.022lb/1000ft^3	Not available	Not Available
Mixer/Loader/Applicator					
(12) mixing/loading and applying liquid with a commercial seed-treatment equipment	No Surrogate data used MRID #447315-01	No	0.006719lb ai/100 lb for Sudangrass	min 132,000 lbs (commercial)	Not Available
				Max 718,000 lbs (commercial)	
			min 0.003906 lb (0.5oz) ai/100lb for wheat and barley	min 132,000 lbs (commercial)	
				max 718,000 lbs (commercial)	
			max 0.01b (1.5 oz) ai/100lb for wheat and barley	min 132,000 lbs (commercial)	
				max 718,000 lbs (commercial)	
(13) mixing/loading and applying seed treatment for on- farm seed treatment.	No Surrogate data used Fenske study	No	min 0.003906 lb (0.5oz) ai/100lb for wheat and barley	12,000	Not Available
			max 0.01b (1.5 oz) ai/100lb for wheat and barley		

[a] Surrogate data are available from seed treatment studies (discussed in the text above) and these data are presented in Appendix A Table A4.

[b] Application rates are the maximum labeled rates found on EPA Reg. Nos.400-438, 773-55, 773-56, 2792-49, 2792-51, 2935-440, 7501-127, 7501-166, 11678-55, 43813-2, 43813-6, 43813-14, 66222-20, CA91001400.

[c] Daily amount treated are based on registrant's estimates of lbs of seed or fruit that would be reasonably expected to be treated in a single day for each exposure scenario of concern. The acres planted per day for on farm seed treatment obtained using a planter with 24 rows and 20 feet wide moving at a speed of 5 mph (assumed 120 lbs of wheat or barley planted per acre) planting an average of 100 acres of wheat or barley per day.
Commercial seed treatment daily lbs treated was provided by registrant. For citrus drencher it was assumed 20 trucks per day and 1200 gallons of imazalil would be mixed for sprayer

[d] Daily gallons mixed or applied for imazalil

Cancer risk assessments for handler were completed by EPA using a baseline exposure scenario and, as needed, increasing levels of risk mitigation (PPE) to achieve cancer risks that are not of concern. Table B in Appendix B of the Occupational and Residential Exposure Assessment Document (Seyed Tadayon) present total cancer risk calculations at baseline and with PPE for each exposure scenario.

The calculations of daily dermal and inhalation exposure to imazalil by handlers were used to calculate the daily dose, and hence the risks, to those handlers.

The following assumptions and factors were used in order to complete this cancer risk assessment:

- The average body weight of 70 kg is used, representing a typical adult.
- Exposure duration is assumed to be 35 years. This represents a typical working lifetime.
- Lifetime is assumed to be 70 years.
- The Q_1^* used in the cancer assessment was $6.11 \times 10^{-2} (mg/kg/day)^{-1}$.
- exposure frequencies used in the calculations are, 250 days for chicken hatcheries (based on the visit to Allen hatcheries in MD), 15 days for commercial seed treatment,10 days on farm seed treatment, and 100 days for commercial citrus applicator.

Since there were no exposure data submitted by the registrant for smoke generators used in chicken hatchery, the air concentration was calculated at the maximum application rate. It was assumed that the handlers were exposed to the smoke generator for a period of one minute. This time period is an estimate based on the label language. It should be noted, however, that smoke may persist in the air after the canister has ceased to smoke. This effect would be minimized by dilution of smoke from the ventilation system and by the fact that the handlers should vacate the setters or hatchers after lighting the smoke generator. The daily dose was calculated both at the baseline (no respirator) and PPE level (organic vapor respirator).

The risk from smoke generator at the maximum application rate is summarized in Table 15.

Table 15: Occupational Handler Short, Intermediate and Long-term inhalation Risk from smoke generator containing Imazalil

Scenario[a]	PF	Air concentration (mg/l)[b]	Short-term Dose[c]	Intermediate-long-term Dose[d]	Short-term MOEs[e]	Intermediate, Long-term MOEs[f]	LADD[g]	Cancer[h]
Smoke generator (baseline)	1 (no respirator)	0.35	0.097	0.083	50	30	2.80e-02	1.7e-03
Smoke generator (PPE)	10 (organic vapor respirator)	0.035	0.0097	0.0083	500	300	2.80e-03	1.7e-04

[a] Baseline represents the use of smoke generator without a respirator
PPE represents the use of smoke generator with an organic vapor respirator

[b] See above calculations

[c] Short-term inhalation dose (mg/kg/day) = airborne concentration of imazalil *inhalation rate (16.6 l/min)/body weight (60kg)

[d] Intermediate-long-term inhalation dose (mg/kg/day) = airborne concentration of imazalil *inhalation rate (16.6 l/min)/body weight (70kg)

[e] Short-term Inhalation MOE = NOAEL (5 mg/kg/day)/ Short-term Daily Inhalation Dose (mg/kg/day).

[f] Intermediate-term Inhalation MOE = NOAEL (2.5 mg/kg/day)/ Intermediate-term Daily Inhalation Dose (mg/kg/day).

[g] LADD (mg/kg/day) = Daily Dose (mg/kg/day) * (Number of days exposure per year (250)) /365 days per year) * 35 years worked/70 year lifetime.

[h] Cancer Risk = LADD (mg/kg/day) * (Q_1*), where Q_1* = $6.11e^{-2}$ (mg/kg/day).

Using the daily dermal exposure scenarios identified in the exposure section, EPA calculated the potential risk to persons from handler exposures and post-application exposures to imazalil.

ii. Occupational Handler Risk Characterization

Table 16 summarizes the MOE values for both the short, intermediate and long -term dermal and inhalation exposure along with cancer risk for occupational handlers. The MOEs are presented for both baseline and PPE. Baseline represents exposure while wearing long pants, long sleeved shirts and no gloves, while using open mixing/loading systems. The PPE represent exposure while wearing long pants, long sleeved shirts and gloves.

The exposure duration for short-term assessments is 1 to 30 days for seed treatment. Intermediate-term durations are greater than 30 days to several months for citrus fruit handlers. Chronic more than 180 days per year for chicken hatcheries have been identified. During the October 24, 2000 meeting HIARC agreed to use short-term NOAEL from a 21-day study for all seed treatment scenarios with exposure duration of less than 30 days.

The results of the **short-term** dermal exposure duration for seed treatment indicate that the MOEs range from 4.33E +02 to 1.45E+05 . A total of 14 MOEs were calculated for the various application rates assessed in each scenario. Based on the minimum level of protection all of the MOEs are > 100.

The results of the **short-term** inhalation exposure duration for seed treatment indicate that the MOEs range from 2.98E+3 to 5.33E+05. A total of 14 MOEs were calculated for the various application rates assessed in each scenario. Based on the minimum level of protection all of the MOEs are > 100.

The results of the **intermediate-term** dermal exposure duration for citrus handlers indicate that the

MOEs range from 3.5E+1 to 4.52E+3. A total of 2 MOEs were calculated. Based on the minimum level (gloves only) of protection all of the MOEs are greater than 100. The results of the **intermediate-term** inhalation exposure duration for citrus handlers show that the MOEs range from 5.46E+3 to 1.94E+04.

The results of the **long-term** dermal exposure duration for egg hatchery handlers indicate that the MOEs range from 1.22E +4 to 1.72E+5 . A total of 4 MOEs were calculated. Based on the minimum level of protection all of the MOEs are greater than 100. The results of the **long-term** inhalation exposure duration for egg hatchery handlers indicate that the MOEs range from 1.83E+4 to 1.21E+7 A total of 4 MOEs were calculated. Based on the minimum level of protection all of the MOEs are >100.

The calculations indicate that cancer risks at **baseline** are in the range of 3.80E-03 to 3.36E-07 and Cancer risks with additional **PPE** are in the range of 5.84E-4 to 1.37E-07 for all the scenarios.

Table 16: Summary of Exposure Variables, MOEs and Cancer Risk Estimates for uses of Imazalil

Exposure Scenario (Scenario #)	Range of Application Rates (lb ai/A)	Amount Handled per Day	Short-Term Dermal MOEs		Intermediate-Term MOEs		Long-term MOEs		Short-Term Inhalation MOEs		Intermediate, Long-Term MOEs		Cancer	
			Base line	PPE	Base line	PPE	Baseline	PPE	Baseline	PPE	Baseline	PPE	Baseline	PPE
Mixer/Loader														
Mixing/loading liquid formulation for on farm seed treatment (1)	0.003906 lb/100 lb	12,000	8.25e+03	NA	NA	NA	NA	NA	5.33e+05	NA	NA	NA	1.63e-05 2.44e-05	1.37e-07 2.05e-07
	0.01 lb/100 lbs		3.20e+03	NA	NA	NA	NA	NA	2.08e+05	NA	NA	NA	4.16e-05 6.24e-05	3.50e-07 5.25e-07
Mixing/loading liquid (EC) for Drencher application (2)	0.6255 lb ai/100 gallons	1,200 gallons	NA	NA	1.24e+02	NA	NA	NA	NA	NA	1.94e+04	NA	1.07e-03	9.55e-06
Mixing/loading liquid (EC) for a waxing equipment (3)	1.665 lb ai/100 gallons	1,600 gallons	NA	NA	3.48e+01	4.52e+03	NA	NA	NA	NA	5.46e+03	NA	3.80e-03	3.40e-05
Mixing/loading Liquid (EC) for a foaming equipment (4)	1.665 lb ai/100 gallons	No Data	NA	NA	No Data	No Data	NA	NA	NA	NA	No Data	No Data	No Data	No Data
Mixing/loading liquid formulation for high pressure hand application (5)	0.00032 lb ai/1000 ft^3	4320ft^3	NA	NA	NA	NA	1.06e+05	NA	NA	NA	1.05e+07	NA	4.92e-07	NA
		37800 ft^3	NA	NA	NA	NA	1.22e+04	NA	NA	NA	1.21e+07	NA	4.30e-06	NA
Applicator														
Applying liquid formulation with a drencher (6)	0.6255 lb ai/100 gallons	1,200 gallons	NA	NA	No Data	No Data	NA	NA	NA	NA	No Data	No Data	No Data	No Data
Applying liquid formulation for a foaming equipment (7)	1.665 lb ai/100 gallons	1,600 gallons	NA	NA	No Data	No Data	NA	NA	NA	NA	No Data	No Data	No Data	No Data
Applying liquid formulation for a waxing equipment (8)	1.665 lb ai/100 gallons	No Data	NA	NA	No Data	No Data	NA	NA	NA	NA	No Data	No Data	No Data	No Data

Exposure Scenario (Scenario #)	Range of Application Rates (lb ai/A)	Amount Handled per Day	Short-Term Dermal MOEs		Intermediate-Term MOEs		Long-term MOEs		Short-Term Inhalation MOEs		Intermediate, Long-Term MOEs		Cancer	
			Base line	PPE	Base line	PPE	Baseline	PPE	Baseline	PPE	Baseline	PPE	Baseline	PPE
Applying liquid formulation with a high pressure handwand sprayer (9)	0.00032 lb ai/1000 ft^3	4320 ft^3	NA	NA	NA	NA	1.72+05	NA	NA	NA	1.61e+05	NA	3.36e-07	NA
		37800 ft^3	NA	NA	NA	NA	1.95e+04	NA	NA	NA	1.83e+04	NA	2.95e-06	NA
Handler for commercial seed treatment (10)	0.00671 lb ai/100 lbs Sudangrass	132,000	8.43e+04	NA	NA	NA	NA	NA	1.88e+05	NA	NA	NA	2.42e-06	3.83-07
		718,000	1.55e+04	NA	NA	NA	NA	NA	3.46e+04	NA	NA	NA	1.31e-05	2.08e-06
	Min 0.00396 lb ai/100lb wheat and barley	132,000	1.45e+05	NA	NA	NA	NA	NA	3.23e+05	NA	NA	NA	1.35e-06	2.23e-07
		718,000	2.66e+04	NA	NA	NA	NA	NA	5.94e+04	NA	NA	NA	7.66e-06	1.21e-06
	Max 0.01lb ai/100 lbs wheat and barley	132,000	5.66e+04	NA	NA	NA	NA	NA	1.26e+05	NA	NA	NA	3.60e-06	5.71e-07
		718,000	1.04e+05	NA	NA	NA	NA	NA	2.32e+04	NA	NA	NA	2.20e-06	3.10e-06
Apply/light smoke canisters (11)	0.022 lb ai/1000 ft^3	No Data	NA	NA	NA	NA	No Data	No Data	NA	NA	No Data	No Data	No Data	No Data
Mixer/ Loader/Applicator														
Mixing/loading and applying liquid with a commercial seed-treatment equipment (12)	0.00671 lb ai/100 lbs Sudangrass	132,000	3.51e+03	NA	NA	NA	NA	NA	2.42e+04	NA	NA	NA	5.74e-05	1.03e-05
		718,000	6.46e+02	NA	NA	NA	NA	NA	4.45e+03	NA	NA	NA	3.14e-04	5.58e-05
	Min 0.00396 lb ai/100lb wheat and barley	132,000	6.03e+03	NA	NA	NA	NA	NA	4.15e+04	NA	NA	NA	3.35e-05	5.98e-05
		718,000	1.11e+03	NA	NA	NA	NA	NA	7.63e+03	NA	NA	NA	1.82e-04	3.25e-05
	Max 0.01lb ai/100 lbs wheat and barley	132,000	2.36e+03	NA	NA	NA	NA	NA	1.62e+04	NA	NA	NA	8.56e-05	1.53e-05
		718,000	4.33e+02	NA	NA	NA	NA	NA	2.98e+03	NA	NA	NA	4.66e-04	8.32e-05

Exposure Scenario (Scenario #)	Range of Application Rates (lb ai/A)	Amount Handled per Day	Short-Term Dermal MOEs		Intermediate-Term MOEs		Long-term MOEs		Short-Term Inhalation MOEs		Intermediate, Long-Term MOEs		Cancer	
			Baseline	PPE	Baseline	PPE	Baseline	PPE	Baseline	PPE	Baseline	PPE	Baseline	PPE
Mixing/loading/ applying seed treatment for on-farm seed treatment (13)	0.003906 lb/100 lb	12,000	See PPE	2.30e+03	NA	NA	NA	NA	See PPE	2.65e+05	NA	NA	See PPE	5.84e-05 8.75e-05
	0.01 lb/100 lbs		See PPE	8.96e+02	NA	NA	NA	NA	See PPE	1.04e+05	NA	NA	See PPE	1.50e-04 2.25e-04

- Short-termDaily Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day)/ Body weight (70 kg).
- intermediate-termDaily Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day)/ Body weight (70 kg)*0.41.
- Short-term Dermal MOE = NOAEL (160 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
- Intermediate-term Dermal MOE = NOAEL (15.8 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
- Short-term Daily Inhalation Dose (mg/kg/day) = Daily Inhalation Exposure (mg/day)/ Body weight (60 kg).
- Intermediate and Long-term Daily Inhalation Dose (mg/kg/day) = Daily Inhalation Exposure (mg/day)/ Body weight (70 kg).
- Short-term Inhalation MOE = NOAEL (5 mg/kg/day)/ Short-term Daily Inhalation Dose (mg/kg/day).
- Intermediate-term Inhalation MOE = NOAEL (2.5 mg/kg/day)/ Intermediate-term Daily Inhalation Dose (mg/kg/day).
- Total Dose (mg/kg/day) =Short-term Daily Dermal Dose (mg/kg/day) + short-term Daily Inhalation Dose (mg/kg/day)
- BaselineLADD (mg/kg/day) = Total Daily Dose (mg/kg/day) * 15 /365 days per year) * 35 years worked/70 year lifetime.
- Baseline Cancer Risk = Baseline LADD (mg/kg/day) * (Q_1*), where Q_1* = $6.11e^{-2}$ (mg/kg/day).
- Baseline dermal unit exposure represents long pants, long sleeved shirt, no gloves, open mixing/loading.
- Baseline inhalation exposure represents no respirator.
- Application rates are maximum rate values found on imazalil labels.
- Daily amount treated values are from the EPA HED and registrant estimates of pounds treated, cubic footage, or gallons that could be treated in a single day for each exposure scenario of concern.
- Daily dermal exposure (mg/day) = Unit Exposure (mg/lb ai) * Appl. rate (lb ai/1000 ft^3, lb ai/100 lb or lb ai/100 gallons) * amount (pounds treated, cubic footage or gallons) treated per day.
- Daily inhalation exposure (mg/day) = Unit Exposure (µg/lb ai) * (1mg/1000 µg) Conversion * Application Rate (lb ai/1000 ft^3, lb ai/100 lb or lb ai/100 gallons) * amount (pounds,cubicfootage or gallons) treated per day.

iii. Citrus Treatment Applicators

HED has insufficient exposure data to provide an assessment of citrus treatment applications (drencher, wax application and foamers). The current mixer/loader surrogate data from PHED were used to address part of this assessment but there is a possible spray drift to workers from using a drencher. The exposure to applicators from waxing and foaming equipment is minimal since these equipment are operated remotely, however the possibility of exposure to the operator needing to enter the area to monitor the operation of the machinery or fix problems which could occur with the machinery still exists. The air monitoring study submitted by the registrant would not address the exposure resulting from the use of a smoke generator in chicken hatcheries and consequently could not be used in this assessment. For smoke generators, a worst case calculation based on the maximum application rate revealed that in order to obtain the target MOE of 100 an organic vapor respirator would be required. For commercial seed treatment, surrogate data was submitted by Uniroyal on behalf of Janssen pharmaceutica in which the assessment is included, but for on-farm seed treatment, the **only** source of data available was a published study by Fenske which utilized a dust formulation which by far has a higher potential for exposure than the imazalil emulsifiable concentrate formulations. HED welcomes a study utilizing the liquid formulation of imazalil for the on-farm seed treatment, but lacking this data, HED has no other choice but to use Fenske's data to assess for this scenario.

Finally, there are possible dermal and inhalation exposures to handlers applying imazalil to air ducts. No chemical-specific or surrogate data are available to assess handler exposure from this specialized use pattern. The Agency estimates that handler dermal and inhalation exposure would be minimal, since the product is diluted with the flow of air current. Even with a vapor pressure of 1.87E-8 mm Hg, the inhalation exposure should be minimal and relatively small amounts of active ingredient are handled per day. Consequently, in lieu of exposure data upon which to assess risk, EPA will require handlers to wear gloves in addition to baseline attire while handling/applying imazalil. Also for the prevention of spray drift from drenching a glass shield is recommended to prevent any possible dermal and inhalation exposure.

iv. Occupational Post-application Exposure

HED has determined that there is potential exposure to persons handling citrus fruits after application is complete (Table 17). The Agency has no data addressing the exposure to workers after the post harvest application of citrus with imazalil. The main activities are sorting/culling/ or packing of products following wax treatment. The estimates of exposure were derived from residue chemistry data, surface area calculations, and a reentry study for citrus found in the scientific literature.

For wax treatment the exposure estimate derived in lieu of data should be considered to be very conservative for the following reasons: (1) it was assumed that all of the imazalil on the treated surface could be transferred to the skin. The chemical is usually part of a wax matrix and quantitative transfer to the skin is unlikely; (2) the transfer coefficients for the hands were obtained from a field study in which contact with contaminated foliage was highly probable; a conveyor belt treatment line would be unlikely to have such a high degree of contact (probably restricted to fingertips only).

Table 17: Imazalil short-term, Intermediate-term and Q*Occupational post application assessment for citrus (waxing only)

Scenario[a]	Dermal Dose[b] (mg/kg/day)	Intermediate -term MOEs[c]	LADD[d]	Cancer[e]
Baseline	0.133	120	1.09e-02	6.68e-04
PPE	0.0133	NA	1.09e-03	6.68e-05

[a] Baseline represents long pants, long sleeved shirt and no gloves
PPE represents long pants, long sleeved shirt and gloves

[b] Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day)/ Body weight (70 kg) x dermal absorption factor (41%) .

[c] Intermediate-term Dermal MOE = NOAEL (15.8 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).

[d] Baseline LADD (mg/kg/day) = Baseline Daily Dose (mg/kg/day) * (Number of days exposure per year (60)) /365 days per year) * 35 years worked/70 year lifetime.
PPE LADD (mg/kg/day) = PPE Daily Dose (mg/kg/day) * (Number of days exposure per year (60)) /365 days per year) * 35 years worked/70 year lifetime.

[e] Baseline Total Cancer Risk = Baseline LADD (mg/kg/day) * (Q_1*), where Q_1* = $6.11e^{-2}$ (mg/kg/day).
PPE Total Cancer Risk = Baseline LADD (mg/kg/day) * (Q_1*), where Q_1* = $6.11e^{-2}$ (mg/kg/day).

Dermal exposure (µg/kg/day) =1500 cm²/hr x 1.9 µg/cm² x 8 hrs/day ÷ 70 kg (bw) x 0.41 (dermal absorption factor)
Dermal exposure (µg/kg/day) =133 µg/kg/day = 0.133 mg/kg/day

At this time, there are no data available to adequately address the return of handlers to hatchers or setters for the purpose of disposing of the used smoke canister (data gap). Frequent disinfection of equipment and air which comes in contact with the shell of the egg is required to prevent Aspergillus molds. CLINFARM EC and smoke generator is used as the last stage in hatchery equipment sanitation program after the removal of one brood and before the introduction of eggs for the next brood in setters or hatchers. Before the eggs are transferred to setters, the shelves and inside parameters of the setters or hatchers are treated with imazalil using a handheld equipment or a smoke generator. Hatchery personnel then transfer the eggs from storage room to setters after the 2 hrs REI observed. Eggs are transferred from storage room to setters via trays and placed on shelves inside the setters. Eggs stay in setters for 18 days until they are ready to be transferred to hatchers. There are no dermal contact with eggs or equipment until eggs are ready to be transferred to hatchers. While in the setters, smoke generators are used to disinfect the air or equipment. The frequency of smoke generator use depends on the severity of the problem. For this assessment, it was assumed that the smoke generator was used every day until the eggs are transferred to the hatchers. Constant air flow through the setters or hatchers mitigates any risk of post-application inhalation exposure. The hatchery workers then transfer the egg trays from the setters to a conveyed belt which transports the eggs through a mechanical vaccination machine. After being vaccinated the egg trays are moved to hatchers. Eggs stay an average of three days in the hatcher. Once the chick is hatched, the shell debris is removed through a vacuum process which requires no dermal contact. Considering the process, HED believes that there is minimal risk involved in dermal or inhalation exposure to imazalil in chicken hatcheries. Therefore no post-application inhalation or dermal risk assessment was performed for reentry following smoke generator or spraying applications in chicken hatcheries. However, based on the low vapor pressure and short half life (118 minutes) of imazalil in the hatchery with adequate ventilation, HED concludes that ventilation of sufficient duration could adequately mitigate re-entering workers inhalation or dermal exposures and risks following smoke generator applications. Once appropriate ventilation has occurred, HED has no reason to conclude that inhalation or dermal exposures to re-entering would be harmful to hatchery handlers.

As there is no study data available on exposure to imazalil residue on treated seed, the exposure has

been estimated using the unit exposure for handling granular formulations in PHED (maximum application rate and lbs treated per day). Due to the method of seed treatment HED has determined that soil-incorporated," post-application agricultural exposure is considered to be negligible as long as the soil is not directly contacted. The exception is farmers handling treated seed. Therefore it was assumed that exposure to treated seed, which has been stored for an indefinite time before use, represented a minimal exposure hazard to the handler. An estimate of the inherent risk from treated seed was conducted for descriptive purposes using relatively conservative assumptions. The results presented in Table 18 should be used only for determining a comparative range of exposure.

Table 18: Imazalil short-term, Intermediate-term and Q* Occupational post Application Assessment for Seed Treatment

Exposure Scenario	Baseline Dermal				Baseline Inhalation					Baseline Cancer	
	Short-term Daily Dose (mg/kg/day)[a]	Int-term Daily Dose (mg/kg/day)[b]	Short-term MOEs[c]	Int.-term MOEs[d]	Short-term Daily Dose (mg/kg/day)[e]	intermediate-term Daily Dose (mg/kg/day)[f]	Short-term MOEs[g]	Int-term MOEs[h]	Total Dose (mg/kg/day)[i]	LADD[j]	Cancer[k]
Mixer/Loader Exposure											
Mixing/loading treated seed	8.62e-03	4.12e-03	1.86e+04	3.83e+03	2.30e-03	1.74e-03	2.46e+03	1.43e+03	1.02e-02	2.13e-04	1.30e-05
Applicator exposure											
Applying treated seed	1.02e-02	4.86e-03	1.54e+04	3.25e+03	1.44e-03	1.23e-03	3.48e+03	2.03e+03	1.16e-02	2.39e-04	1.46e-05

a Short-termDaily Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day)/ Body weight (70 kg).
b intermediate-termDaily Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day)/ Body weight (70 kg)*0.41.
c Short-term Dermal MOE = NOAEL (160 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
d Intermediate-term Dermal MOE = NOAEL (15.8 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
e Short-term Daily Inhalation Dose (mg/kg/day) = Daily Inhalation Exposure (mg/day)/ Body weight (60 kg).
f Intermediate and Long-term Daily Inhalation Dose (mg/kg/day) = Daily Inhalation Exposure (mg/day)/ Body weight (70 kg).
g Short-term Inhalation MOE = NOAEL (5 mg/kg/day)/ Short-term Daily Inhalation Dose (mg/kg/day).
h Intermediate-term Inhalation MOE = NOAEL (2.5 mg/kg/day)/ Intermediate-term Daily Inhalation Dose (mg/kg/day).
I Total Dose (mg/kg/day) =Short-term Daily Dermal Dose (mg/kg/day) + short-term Daily Inhalation Dose (mg/kg/day)
J BaselineLADD (mg/kg/day) = Total Daily Dose (mg/kg/day) * 15 /365 days per year) * 35 years worked/70 year lifetime.
k Baseline Cancer Risk = Baseline LADD (mg/kg/day) * (Q_1*), where Q_1* = $6.11e^{-2}$ (mg/kg/day).

v. Residential Handler Exposure

Due to imazalil use profile, HED has concluded that there is a low potential for residential exposure.

V. AGGREGATE AND CUMULATIVE EXPOSURE AND RISK CHARACTERIZATION

A. Acute Aggregate Risk

There are no registered residential uses of imazalil, so aggregation would contain only food and water risk estimates.

Acute aggregate risk estimates do not exceed HED's level of concern (aPAD of 0.017 mg/kg/day). The estimated environmental concentrations (EECs) for surface water (GENEEC) were less than the acute DWLOCs, indicating that acute aggregate exposure to imazalil in food and water is less than HED's level of concern. The acute DWLOC for Females 13-50 years is 500 ppb. The EECs for groundwater (SCI-GROW) were less than the acute DWLOC's, indicating that acute aggregate exposure to imazalil in food and water is less than HED's level of concern. The peak GENEEC EEC was 0.072 ppb, while the estimated groundwater EEC was negligible.

B. Chronic Aggregate Risk

Chronic (noncancer) aggregate risk estimates do not exceed HED's level of concern. There is no residential component to the aggregate risk because use of imazalil in residential settings is not expected. Risk contributed by the consumption of food is quite small: <3% of the cPAD for all population subgroups using anticipated residue and percent-crop-treated data. The EECs for surface water (GENEEC) were less than the chronic DWLOCs, indicating that chronic exposure to imazalil in food and water is less than HED's level of concern. The EECs for groundwater (SCI-GROW) were less than the chronic DWLOC's, indicating that chronic exposure to imazalil in food and water is less than HED's level of concern.

C. Cancer Aggregate Risk

Cancer DWLOCs were not calculated since cancer risk from food alone is 2.1×10^{-6}, (1×10^{-6} is considered the negligible risk level for cancer. Any dietary contribution from drinking water would result in risks exceeding 2.1×10^{-6}. It should be noted that EFED concluded that "imazalil is unlikely to contaminate surface and ground waters".

D. Cumulative Exposure and Risk

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact

experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe. For risk assessment purposes, HED has not assumed that imazalil has a common mechanism of toxicity with any other chemical.

VI. RISK CHARACTERIZATION

The imazalil risk assessment contains strengths, weaknesses, and uncertainties based on the existing toxicological and exposure data, modeling methodologies, data gaps, and gaps in scientific knowledge. This assessment uses standard assumptions regarding human body weight, work life, and other exposure parameters; and interspecies extrapolation to estimate risks. Additional assumptions were made regarding route to route extrapolation. Strengths and uncertainties of the assessment are described below.

The toxicological data base for Imazalil is partly adequate for hazard characterization. Data gaps exist for an acute, subchronic and developmental neurotoxicity studies in rats. In acute toxicity studies imazalil is moderately toxic by the oral route (Category II), and is of low toxicity by the dermal (Category III) and inhalation routes (Category IV). It is a severe eye irritant (Category I) but not a dermal irritant (Category IV) or a skin sensitizer. Acute toxic effects are lethargy, ptosis (drooping of the upper eyelids), decreased respiratory rate and gasping respiration, and ataxia.

The toxicity endpoints used in this document to assess hazards include acute dietary and chronic dietary reference doses (RfDs), and short-, intermediate- and long-term dermal and inhalation no observable adverse affect levels (NOAELs)

The thyroid and the liver are primary target organs of imazalil toxicity. Enlarged livers, increased liver weights and liver to body weight ratios, increased centrilobular swollen hepatocytes and increased vacuolization in hepatocytes were seen in one or more laboratory species following subchronic exposures. In chronic dietary exposure of rats, there was an increased incidence of intra cytoplasmic inclusion bodies of hepatocytes, increased severity of hepatocyte vacuolization as well as bile duct proliferation at 16 mg/kg/day. Liver histopathologic lesions were also seen in a 23-month study in mice at 28 mg/kg/day. Increased liver vacuolization was also seen in male rats in a 2-generation reproduction study at 80 mg/kg/day. Increased liver weights were seen in dogs treated for one year at 20 mg/kg/day. The absolute and relative weight of thyroid glands was increased in male rats fed imazalil for two years at $\geq$66 mg/kg/day. Microscopic changes were also seen in the affected thyroids.

The data submitted to the Agency as well as those from the published literature do not demonstrate increased sensitivity of rats, mice, or rabbits from *in utero* exposure to imazalil. Developmental effects in fetuses occurred at or above doses that caused maternal toxicity. In a 2-generation reproduction study in rats, an increased susceptibility of the pups to imazalil was reported. The pup survival rate was adversely affected by imazalil treatment from birth to post natal day 4 in the F2 generation at the highest tested of 80 mg/kg/day.

Carcinogenicity studies in rodents indicate that imazalil is carcinogenic to male Swiss albino mice and male Wistar rats, based on a significant increase in liver adenomas and combined adenomas/carcinomas. In rats there was also an increased incidence of combined thyroid follicular cell adenomas/carcinomas. Imazalil is classified by the CARC in the category “Likely to be carcinogenic in humans” according to

the July 1999 Draft Guidelines for Carcinogenic Assessment. The Committee reaffirmed its earlier decision by recommending a linear low-dose (Q_1^*) extrapolation for quantification of human cancer risk. This extrapolation is supported by the lack of confirmation of the mode of action. The most potent unit risk, $Q_1^*(mg/kg/day)^{-1}$ for imazalil based on male mouse liver adenoma and/or carcinoma combined tumor rates is 6.1×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents (HED Doc 013842).

Imazalil was non mutagenic both *in vivo* and *in vitro* mutagenicity assays.

The Food Quality Protection Act (FQPA) Safety Factor Committee (SFC) evaluated imazalil toxicity and exposure databases and retained a 10x for assessing chronic dietary exposure and reduced it to 3x for acute scenarios. The FQPA SFC concluded that the full safety factor of 10 should be retained for chronic exposure scenarios because of qualitative evidence of increased susceptibility following pre-/postnatal exposure to imazalil in the 2-generation reproduction study in rats and because of a data gap for a developmental neurotoxicity study. Although there was a lack of evidence of susceptibility in the rat/rabbit developmental studies, the data gap for a developmental neurotoxicity study was also considered to apply for acute scenarios, and accordingly the SFC did not completely remove the FQPA factor but reduced it to 3x for acute scenarios.

The dietary exposure analyses is a highly refined Tier 3 assessment since % CT and PDP monitoring data were used in the analyses. Imazalil is used as a post-harvest treatment on citrus and banana. The analytical method used by USDA in data collection analyzes for imazalil *per se*; therefore, an adjustment factor of 1.4 (to account for total residues of imazilil plus the metabolite R014821) derived from an orange study on the nature of the residue was applied. This adjustment factor was translated to all citrus. PDP data for banana were translated to plantain. PDP data for wheat were translated to barley. Imazalil residues in milk food forms were considered to be negligible or zero, and were excluded from the dietary exposure analysis.

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys, (e.g., nursing and non-nursing infants or Hispanic females). Therefore, risks estimated for these population subgroups were included in representative populations having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years).

Considering these uncertainties, the estimated acute dietary risk is not of concern. Use of USDA Pesticide Data Program (PDP) monitoring data, and calculated livestock anticipated residues (ARs) results in a maximum dietary risk estimate of 34 % of the aPAD (for children (1-6 years) at the 99.9^{th} percentile). Acute dietary risk for females of child-bearing age (13-50) was estimated to be 15% of the aPAD.

Estimated chronic dietary exposure is also below HED's level of concern. Use of PDP monitoring data and calculated livestock ARs results in a maximum risk of 3 % of the chronic PAD for children 1-6, the most highly exposed population subgroup. Dietary risk for the general US population was estimated to be 2 % cPAD.

Estimated chronic dietary exposure for the general US population is 0.000034 mg/kg/day, based on use of PDP monitoring data and calculated livestock ARs. This exposure corresponds to a lifetime cancer risk estimate of $2.1 \text{ X } 10^{-6}$ which exceeds HED's level of concern for cancer dietary exposure estimates

of 1.0 x 10^{-6} for the general US population. The Critical Commodity Contribution Analysis indicated that orange and grapefruit food forms were several of the major contributors to the cancer dietary risk estimate accounting for approximately 2/3rd of the dietary exposure.

Imazalil is unlikely to contaminate surface and ground waters. Fate studies show that this chemical is immobile (average K_{oc} = 4,324 mL/g; average K_d = 130 mL/g) and is not expected to move offsite when used as a seed treatment. Both surface and ground water simulations (described later) showed that imazalil may reach drinking water supplies only at very low concentrations.

Acute drinking water levels of concern (DWLOCs) were calculated based on the acute dietary (food) exposure, default body weights and water consumption figures. The acute DWLOC for females 13-50 years is 500 ppb. The estimated environmental concentrations (EECs) for surface water (GENEEC) and groundwater (SCI-GROW) were less than the acute DWLOC's, indicating that acute aggregate exposure to imazalil in food and water is less than HED's level of concern. The peak GENEEC EEC was 0.072 ppb, while the estimated groundwater EEC was negligible.

The EECs for surface water (GENEEC, 0.013 ppb) and groundwater (SCI-GROW, 0 ppb) were less than the chronic DWLOC (87 ppb for general population and 25 ppb for children 1-6 years), indicating that chronic exposure to imazalil in food and water is less than HED's level of concern.

Cancer DWLOCs were not calculated since the dietary cancer risk estimate slightly exceeds the level of concern of $1x10^{-6}$. Therefore, drinking water combined with dietary consumption will be likely above HED's level of concern for purposes of this risk assessment. It should be noted that EFED concluded that "imazalil is unlikely to contaminate surface and ground waters".

Risk assessmsnts from occupational exposure indicate that all exposure scenarios provide MOEs greater than or equal to 100 at baseline attire (i.e., long pants, long sleeved shirts, no gloves) for seed handlers (short term dermal 1-30 days), for intermediate-term dermal assessments (100 days assumed) for citrus handlers except for mixing/loading liquid formulation for waxing equipment and for long-term dermal assessments (250 days assumed) for chicken hatchery handlers. The short, intermediate and long-term inhalation assessment indicates that the all exposure scenarios provide MOEs greater than or equal to 100 at baseline attire (i.e, no respirator). The intermediate-term dermal assessments (100 days assumed) for citrus handler indicate that the all exposure scenarios provide MOEs greater than or equal to 100 at PPE (i.e., long pants, long sleeved shirts, gloves).

Based on the low vapor pressure and short half life (118 minutes) of imazalil following smoke generator or spraying applications in chicken hatcheries and subsequent ventilation for sufficient duration, post-application dermal or inhalation risk assessment for hatchery handlers was not required.

Post application exposure to imazalil from treated seeds following soil incorporation is considered to be negligible as long as the soil is not directly contacted. Farmers handling treated seed which has been stored for an indefinite time before use, represented a minimal exposure hazard to the handler.

There are no registered residential uses of imazalil and thus residential exposure is not expected. Aggregation would include only food and water risk estimates. Acute aggregate risk estimates do not exceed HED's level of concern (aPAD of 0.017 mg/kg/day). Chronic aggregate risk estimates do not exceed HED's level of concern. An aggregate cancer assessment was not done because the cancer risk

from food alone was estimated to exceed $1x10^{-6}$.

VII. DATA NEEDS

Additional date requirements have been identified in the attached Science Chapters and are summarized here.

Toxicology Data for OPPTS Guidelines:

- 870.6300 Developmental Neurotoxicity in Rats
- 870.6200 Acute Neurotoxicity Study in Rats
- 870.6200 Subchronic Neurotoxicity Study in rats

Product and Residue Chemistry Data for OPPTS Guidelines:

- 860.1200 Directions for Use
- 860.1340 Residue analytical Method - Animal Commodities
- 860.1360 Multiresidue Method
- 860.1480 Egg and poultry fumigation Study

Occupational Exposure Data for OPPTS Guidelines

- Exposure study of citrus treatment applicators (wax application and foamers)
- Post application inhalation and dermal exposure following smoke generator or spraying applications in chicken hatcheries

VIII. ATTACHMENTS

Report of the Hazard Identification Assessment Review Committee. Abdallah Khasawinah (6/29/1999, HED DOC #013539)
Report of the FQPA Safety Factor Committee. Brenda Tarplee (9/28/1999, HED DOC #013762)
Report of the Cancer Assessment Review Committee- Imazalil. SanJivani Diwan (12/7/99, HED DOC #013885)
Product and Residue Chemistry Chapter. Thurston Morton, David E. Hrdy (1/31/2002, D272790)
Toxicology Chapter. Abdallah Khasawinah (1/31/2002, HED DOC# 0050434)
Occupational and Residential Exposure Assessment. Seyed Tadayan 124/25/2000, D270918)
Dietary Exposure and Risk Estimates for Reregistraiton. Thurston Morton, David E. Hrdy (1/24/2002, D280449)
Environmental Fate and Effects Chapter. Larry Liu and Richard Lee (2000, D250028)